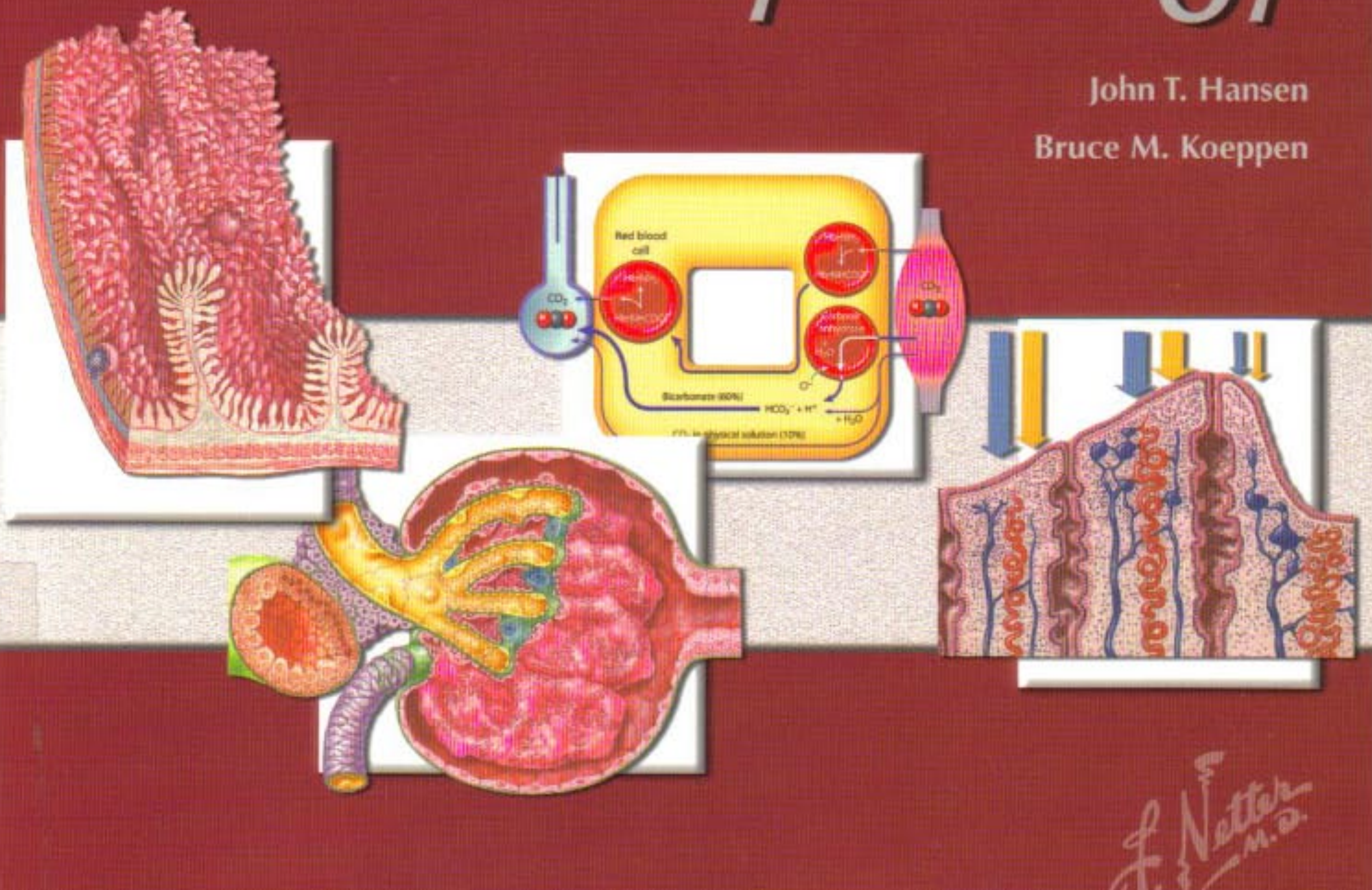
Netter's Atlas of Human Physiology

John T. Hansen
Bruce M. Koeppen


Red blood cell
CO_2
Cl^-
Bicarbonate (60%)
$HCO_3^- + H^+$
$+ H_2O$
CO_2 in physical solution (10%)
CO_2

F. Netter M.D.

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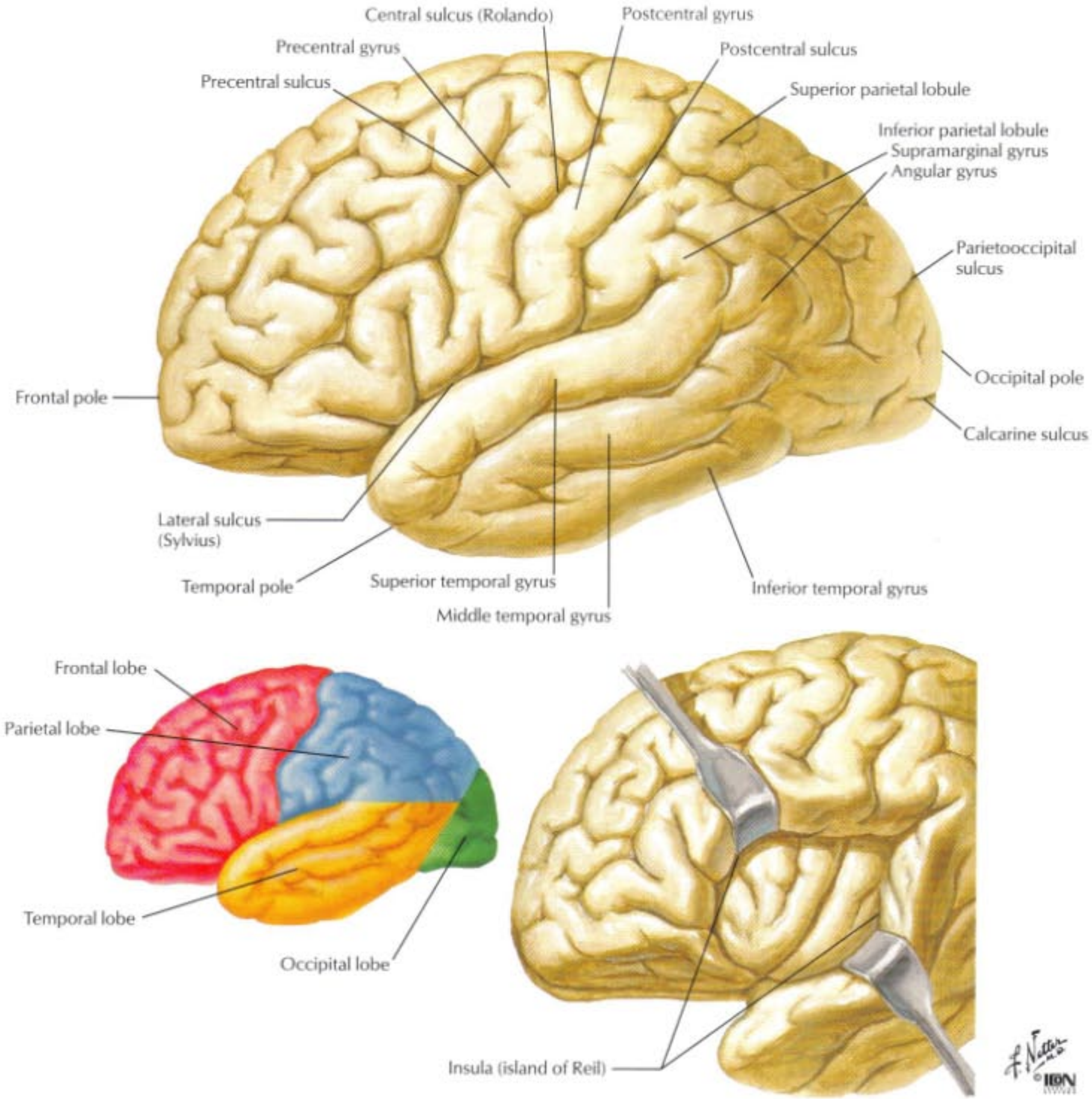
Central sulcus (Rolando)
Postcentral gyrus
Precentral gyrus
Postcentral sulcus
Precentral sulcus
Superior parietal lobule
Inferior parietal lobule
Supramarginal gyrus
Angular gyrus
Parietooccipital sulcus
Occipital pole
Calcarine sulcus
Frontal pole
Lateral sulcus (Sylvius)
Temporal pole
Superior temporal gyrus
Middle temporal gyrus
Inferior temporal gyrus
Frontal lobe
Parietal lobe
Temporal lobe
Occipital lobe
Insula (island of Reil)

FIGURE 2.1 ORGANIZATION OF THE BRAIN: CEREBRUM

The cerebral cortex represents the highest center for sensory and motor processing. In general, the frontal lobe processes motor, visual, speech, and personality modalities. The parietal lobe processes sensory information; the temporal lobe, auditory and memory modalities; and the occipital lobe, vision. The cerebellum coordinates smooth motor activities and processes muscle position. The brainstem (medulla, pons, midbrain) conveys motor and sensory information and mediates important autonomic functions. The spinal cord receives sensory input from the body and conveys somatic and autonomic motor information to peripheral targets (muscles, viscera).

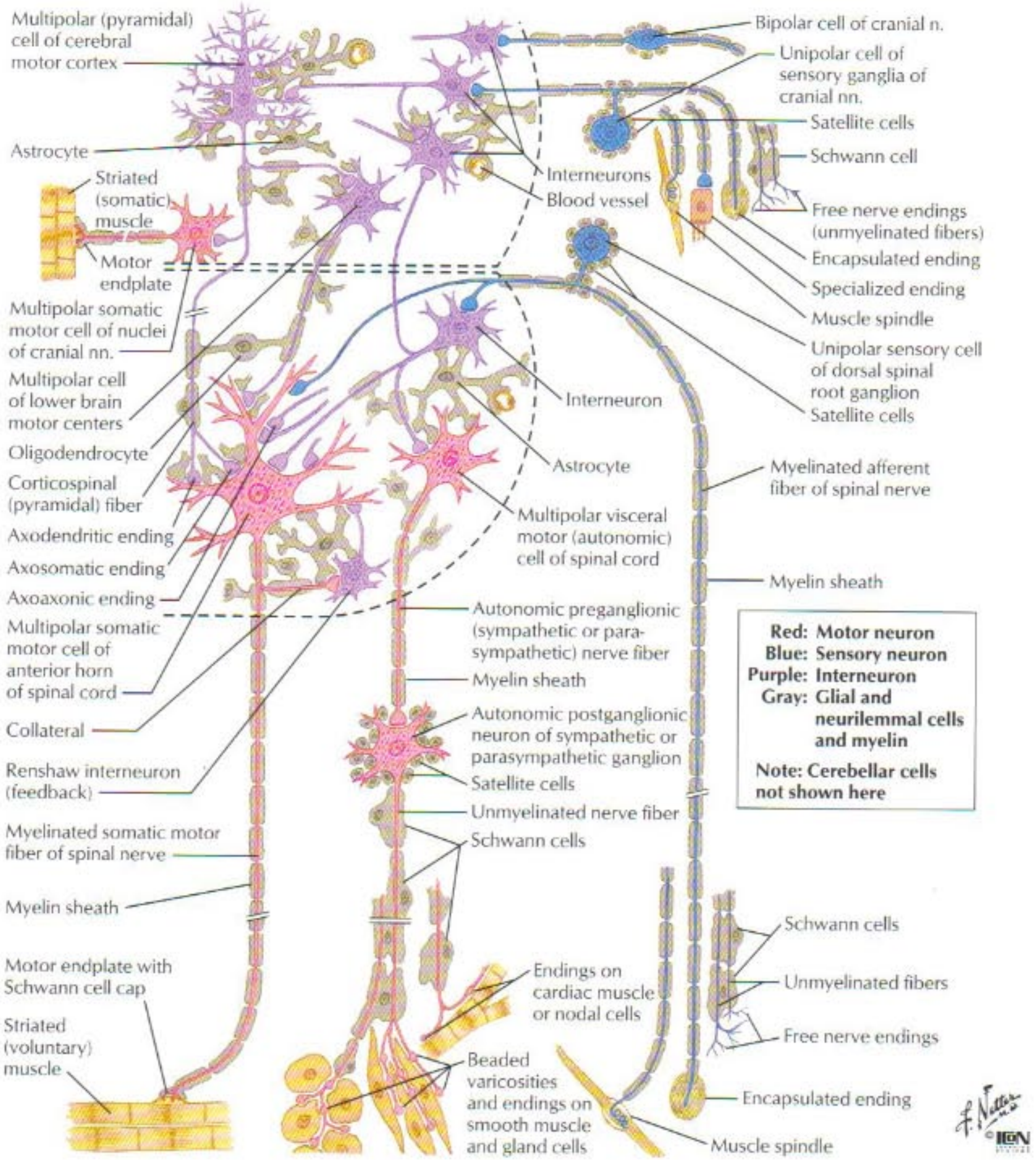
Multipolar (pyramidal) cell of cerebral motor cortex
Astrocyte
Striated (somatic) muscle
Motor endplate
Multipolar somatic motor cell of nuclei of cranial nn.
Multipolar cell of lower brain motor centers
Oligodendrocyte
Corticospinal (pyramidal) fiber
Axodendritic ending
Axosomatic ending
Axoaxonic ending
Multipolar somatic motor cell of anterior horn of spinal cord
Collateral
Renshaw interneuron (feedback)
Myelinated somatic motor fiber of spinal nerve
Myelin sheath
Motor endplate with Schwann cell cap
Striated (voluntary) muscle
Interneurons
Blood vessel
Interneuron
Astrocyte
Multipolar visceral motor (autonomic) cell of spinal cord
Autonomic preganglionic (sympathetic or parasympathetic) nerve fiber
Myelin sheath
Autonomic postganglionic neuron of sympathetic or parasympathetic ganglion
Satellite cells
Unmyelinated nerve fiber
Schwann cells
Endings on cardiac muscle or nodal cells
Beaded varicosities and endings on smooth muscle and gland cells
Bipolar cell of cranial n.
Unipolar cell of sensory ganglia of cranial nn.
Satellite cells
Schwann cell
Free nerve endings (unmyelinated fibers)
Encapsulated ending
Specialized ending
Muscle spindle
Unipolar sensory cell of dorsal spinal root ganglion
Satellite cells
Myelinated afferent fiber of spinal nerve
Myelin sheath
Red: Motor neuron
Blue: Sensory neuron
Purple: Interneuron
Gray: Glial and neurilemmal cells and myelin
Note: Cerebellar cells not shown here
Schwann cells
Unmyelinated fibers
Free nerve endings
Encapsulated ending
Muscle spindle
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FIGURE 2.2 ORGANIZATION OF THE BRAIN: CELL TYPES

Neurons form the functional cellular units responsible for communication, and throughout the nervous system, they are characterized by their distinctive size and shapes (e.g., bipolar, unipolar, multipolar). Supporting cells include the neuroglia (e.g., astrocytes, oligodendrocytes), satellite cells, and other specialized cells that optimize neuronal function, provide maintenance functions, or protect the nervous system.

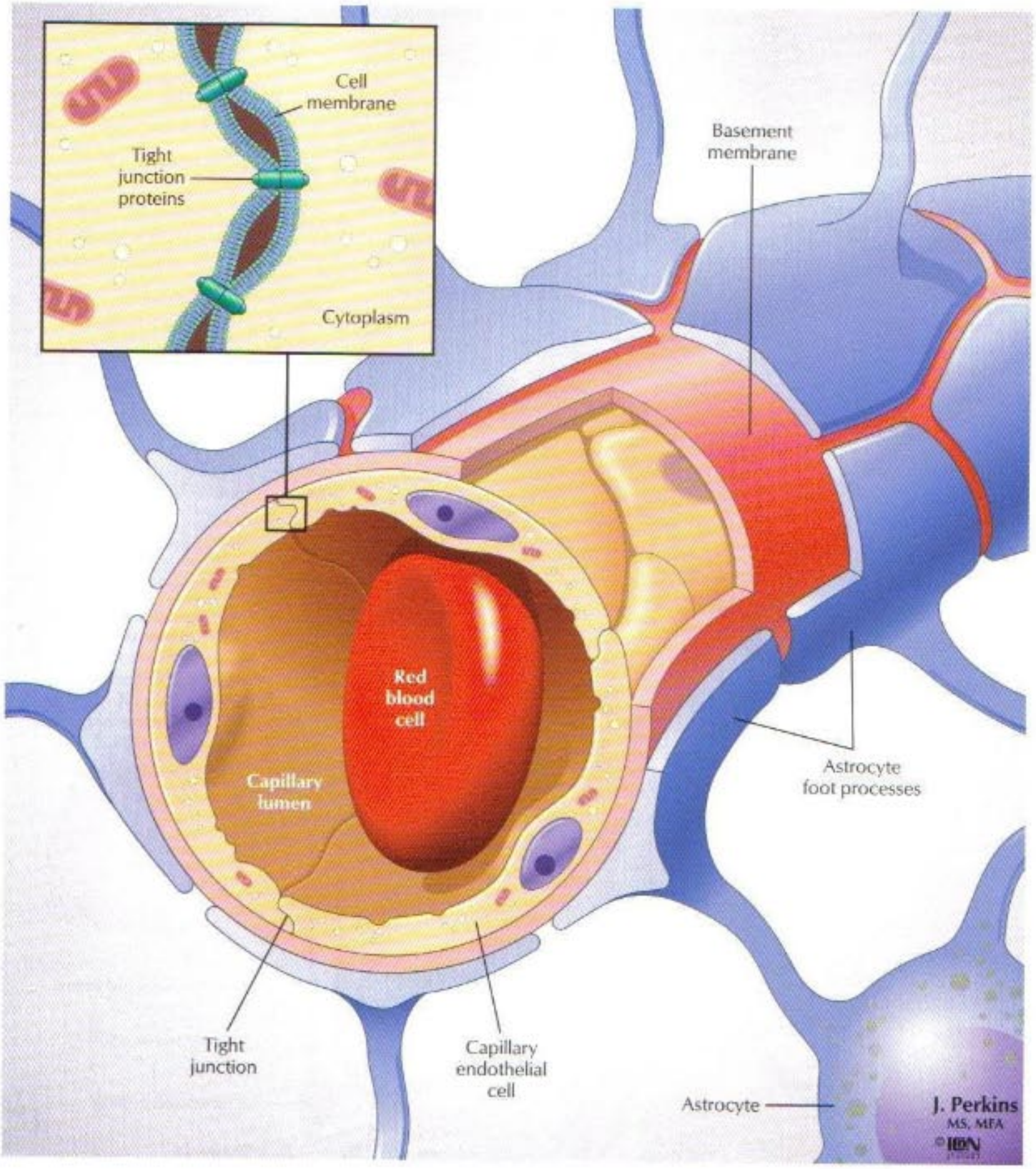
Cell membrane
Tight junction proteins
Cytoplasm
Basement membrane
Red blood cell
Capillary lumen
Astrocyte foot processes
Tight junction
Capillary endothelial cell
Astrocyte
J. Perkins
MS, MFA
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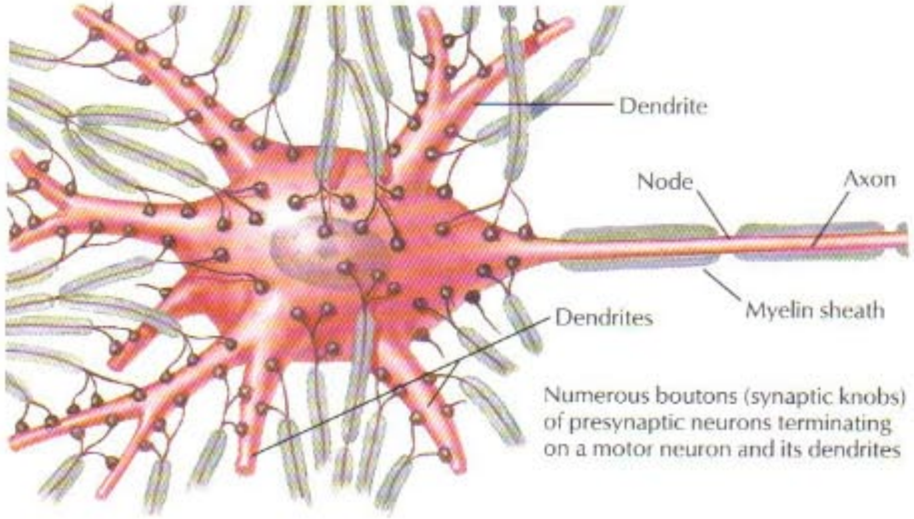
FIGURE 2.3 BLOOD-BRAIN BARRIER

The blood-brain barrier (BBB) is the cellular interface between the blood and the central nervous system (CNS: brain and spinal cord). It serves to maintain the interstitial fluid environment to ensure optimal functionality of the neurons. This barrier consists of the capillary endothelial cells with an elaborate network of tight junctions and astrocytic foot processes that abut the endothelium and its basement membrane. The movement of large molecules and other substances (including many drugs) from the blood to the interstitial space of the CNS is restricted by the BBB. CNS endothelial cells also exhibit a low level of pinocytotic activity across the cell, so specific carrier systems for the transport of essential substrates of energy and amino acid metabolism are characteristic of these cells. The astrocytes help transfer important metabolites from the blood to the neurons and also remove excess K^+ and neurotransmitters from the interstitial fluid.


Dendrite
Node
Axon
Dendrites
Myelin sheath

Numerous boutons (synaptic knobs) of presynaptic neurons terminating on a motor neuron and its dendrites

Enlarged section of bouton

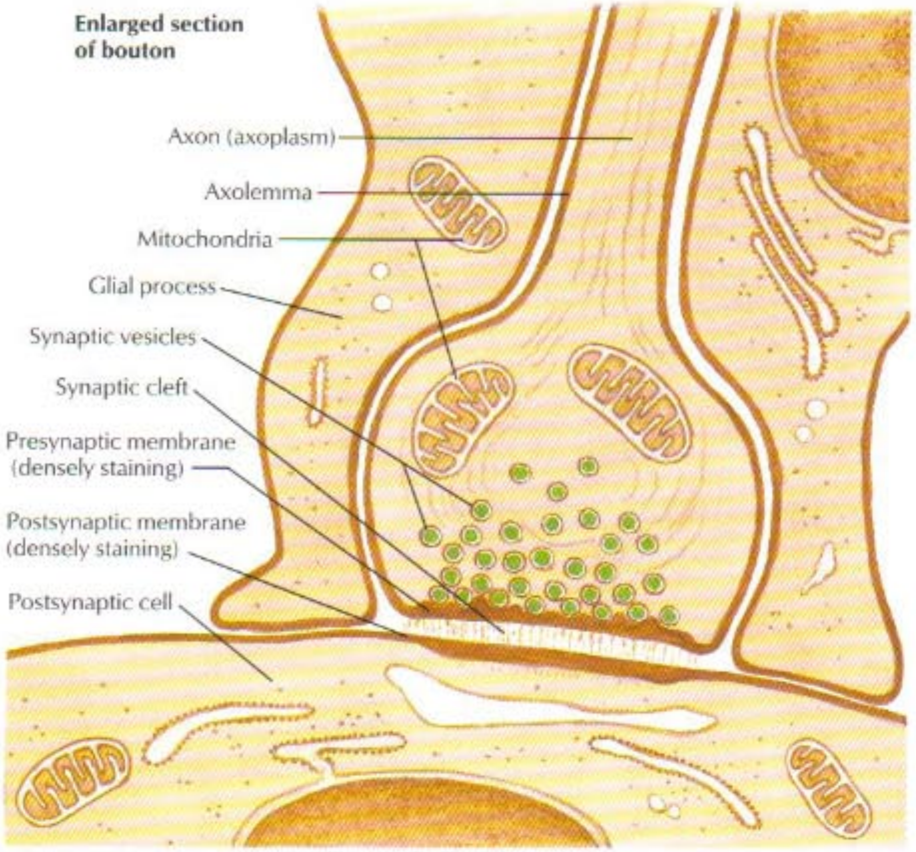

Axon (axoplasm)
Axolemma
Mitochondria
Glial process
Synaptic vesicles
Synaptic cleft
Presynaptic membrane (densely staining)
Postsynaptic membrane (densely staining)
Postsynaptic cell

FIGURE 2.4 MORPHOLOGY OF SYNAPSES

Neurons communicate with each other and with effector targets at specialized regions called synapses. The top figure shows a typical motor neuron that receives numerous synaptic contacts on its cell body and associated dendrites. Incoming axons lose their myelin sheaths, exhibit extensive branching, and terminate as synaptic boutons (synaptic terminals or knobs) on the motor neuron. The lower figure shows an enlargement of one such synaptic bouton. Chemical neurotransmitters are contained in synaptic vesicles, which can fuse with the presynaptic membrane, release the transmitters into the synaptic cleft, and then bind to receptors situated in the postsynaptic membrane. This synaptic transmission results in excitatory, inhibitory, or modulatory effects on the target cell.

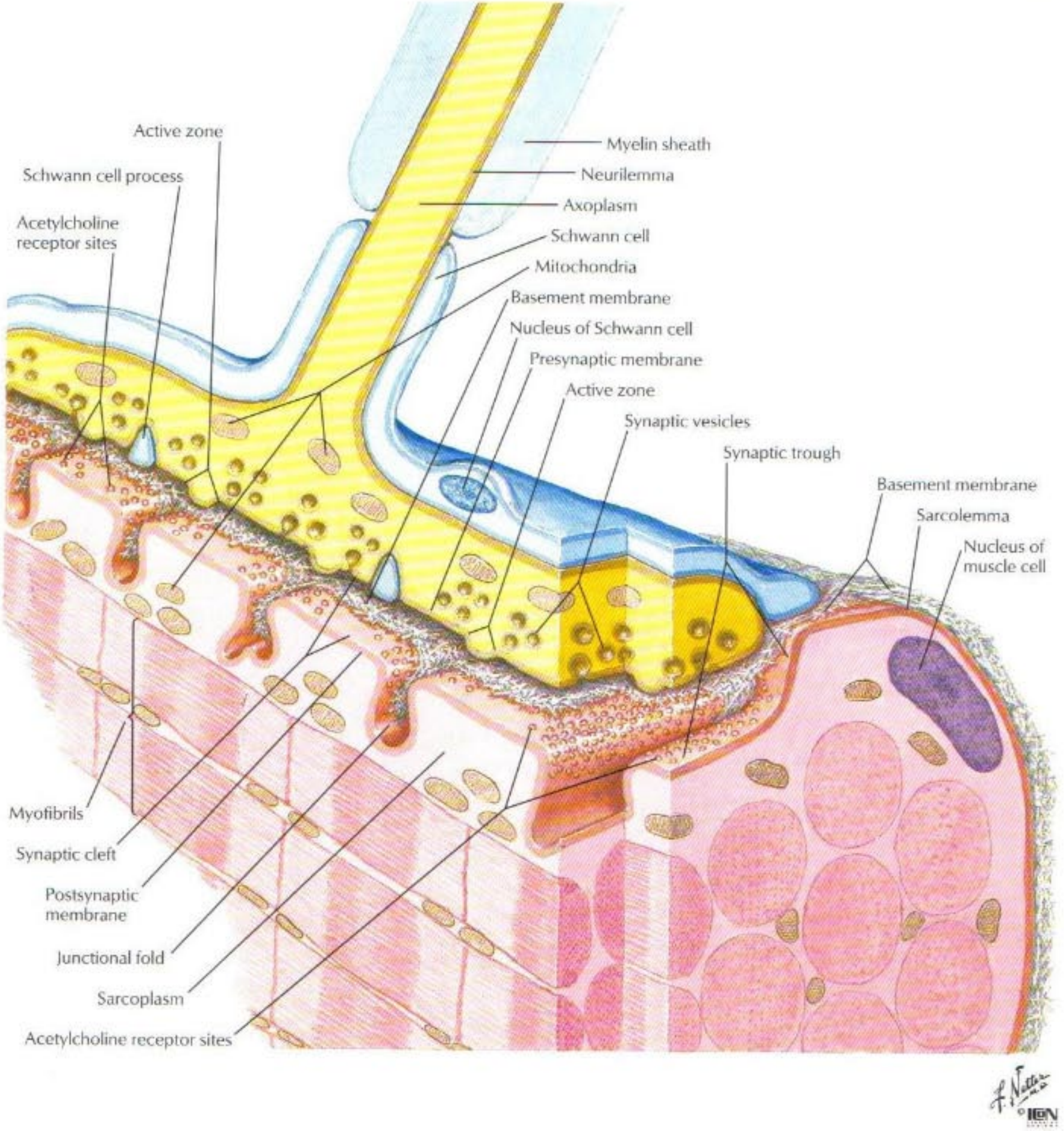

Active zone
Schwann cell process
Acetylcholine receptor sites
Myelin sheath
Neurilemma
Axoplasm
Schwann cell
Mitochondria
Basement membrane
Nucleus of Schwann cell
Presynaptic membrane
Active zone
Synaptic vesicles
Synaptic trough
Basement membrane
Sarcolemma
Nucleus of muscle cell
Myofibrils
Synaptic cleft
Postsynaptic membrane
Junctional fold
Sarcoplasm
Acetylcholine receptor sites
F. Netter
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FIGURE 2.5 STRUCTURE OF THE NEUROMUSCULAR JUNCTION

Motor axons that synapse on skeletal muscle form expanded terminals called neuromuscular junctions (motor endplates). The motor axon loses its myelin sheath and expands into a Schwann cell–invested synaptic terminal that resides within a trough in the muscle fiber. Acetylcholine-containing synaptic vesicles accumulate adjacent to the presynaptic membrane and, when appropriately stimulated, release their neurotransmitter into the synaptic cleft. The transmitter then binds to receptors that mediate depolarization of the muscle sarcolemma and initiate a muscle action potential. A single muscle fiber has only one neuromuscular junction, but a motor axon can innervate multiple muscle fibers.

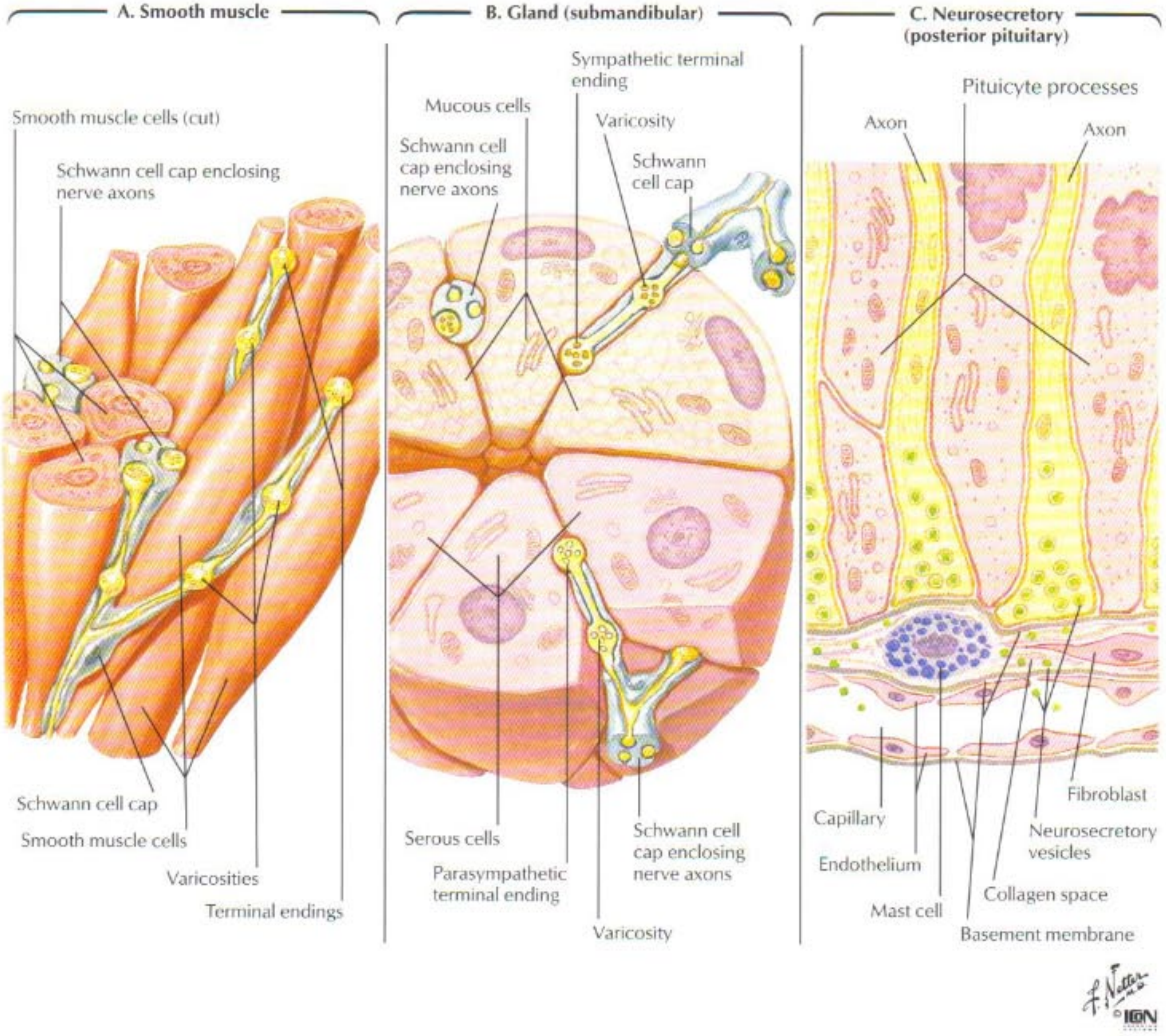
A. Smooth muscle
Smooth muscle cells (cut)
Schwann cell cap enclosing nerve axons
Schwann cell cap
Smooth muscle cells
Varicosities
Terminal endings
B. Gland (submandibular)
Sympathetic terminal ending
Mucous cells
Varicosity
Schwann cell cap enclosing nerve axons
Schwann cell cap
Serous cells
Parasympathetic terminal ending
Schwann cell cap enclosing nerve axons
Varicosity
C. Neurosecretory (posterior pituitary)
Pituicyte processes
Axon
Axon
Fibroblast
Capillary
Neurosecretory vesicles
Endothelium
Collagen space
Mast cell
Basement membrane
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FIGURE 2.6 VISCERAL EFFERENT ENDINGS

Neuronal efferent endings on smooth muscle (A) and glands (B and C) exhibit unique endings unlike the presynaptic and postsynaptic terminals observed in neuronal and neuromuscular junction synapses. Rather, neurotransmitter substances are released into interstitial spaces (A and B) or into the bloodstream (C, neurosecretion) from expanded nerve terminal endings. This arrangement allows for the stimulation of numerous target cells over a wide area. Not all smooth muscle cells are innervated. They are connected to adjacent cells by gap junctions and can therefore contract together with the innervated cells.

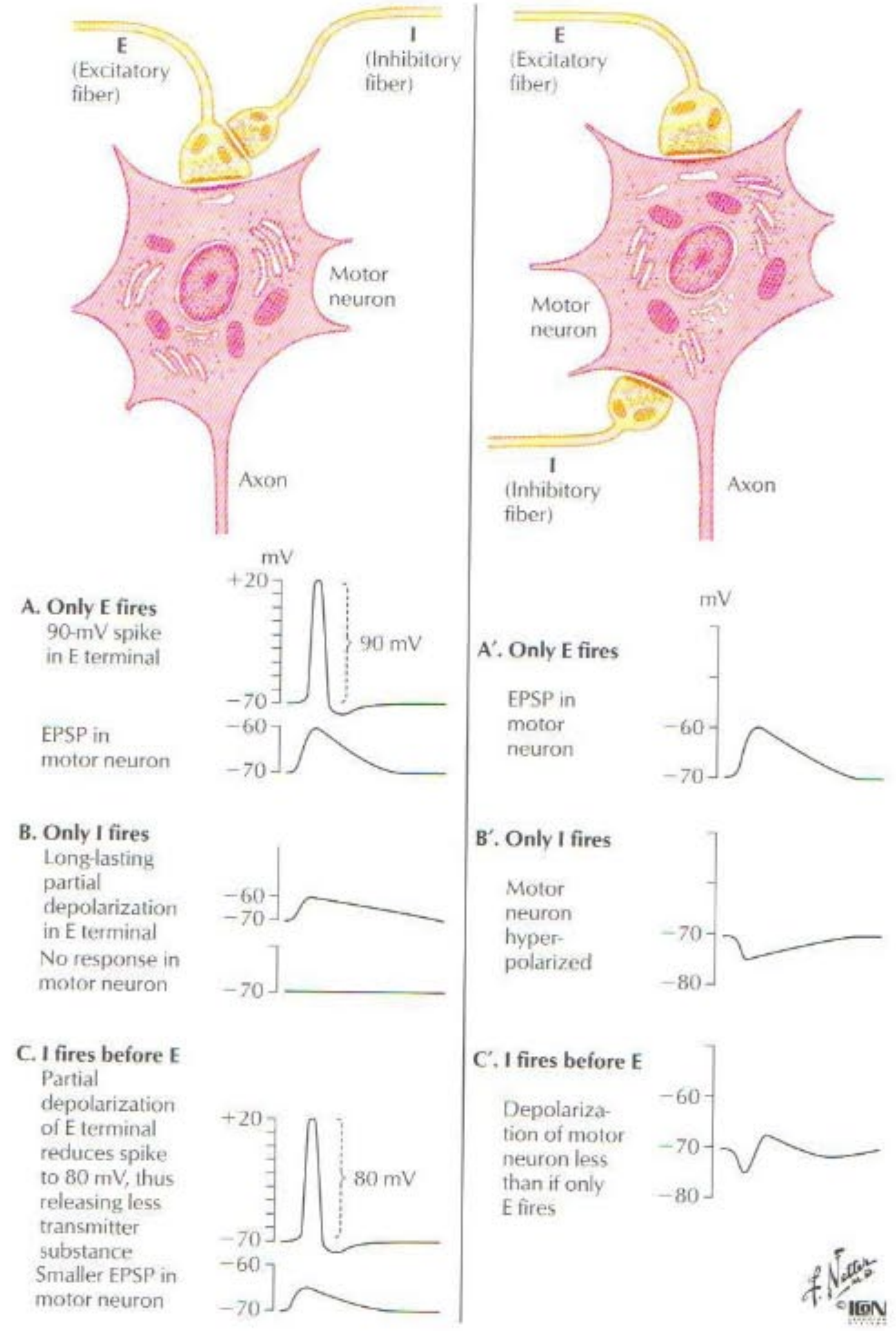
E
(Excitatory fiber)
I
(Inhibitory fiber)
Motor neuron
Axon
E
(Excitatory fiber)
Motor neuron
I
(Inhibitory fiber)
Axon
mV
+20
90 mV
−70
−60
−70
A. Only E fires
90-mV spike in E terminal
EPSP in motor neuron
B. Only I fires
Long-lasting partial depolarization in E terminal
−60
−70
No response in motor neuron
−70
C. I fires before E
Partial depolarization of E terminal reduces spike to 80 mV, thus releasing less transmitter substance
+20
80 mV
−70
−60
Smaller EPSP in motor neuron
−70
mV
A′. Only E fires
EPSP in motor neuron
−60
−70
B′. Only I fires
Motor neuron hyper-polarized
−70
−80
C′. I fires before E
−60
Depolarization of motor neuron less than if only E fires
−70
−80
F. Netter
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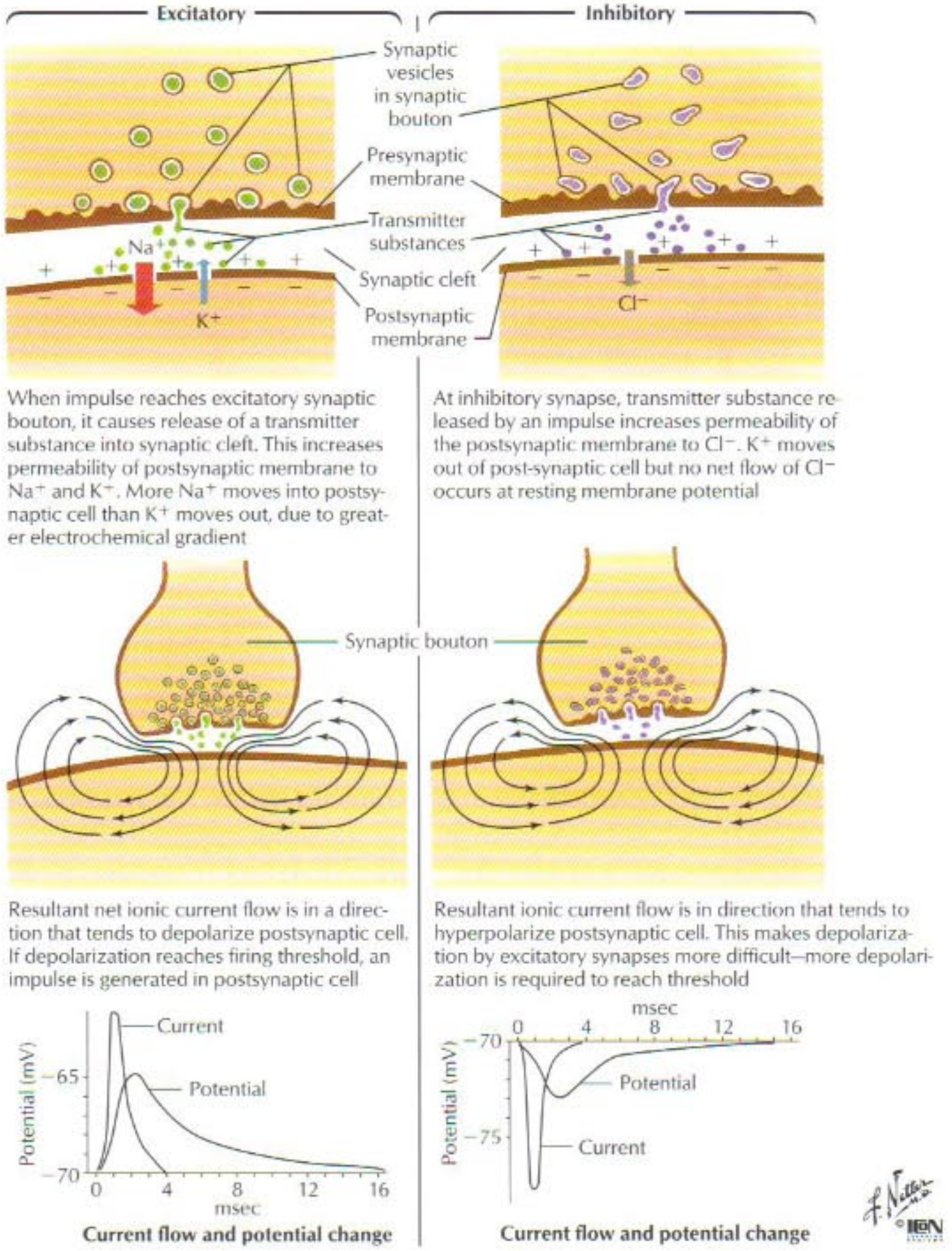
FIGURE 2.7 SYNAPTIC INHIBITORY MECHANISMS

Inhibitory synapses modulate neuronal activity. Illustrated here is presynaptic inhibition (left panel) and postsynaptic inhibition (right panel) at a motor neuron.


Excitatory
Inhibitory
Synaptic vesicles in synaptic bouton
Presynaptic membrane
Transmitter substances
Synaptic cleft
Postsynaptic membrane
Na+
K+
Cl−
Synaptic bouton
Current
Potential
Potential (mV)
−65
−70
−75
0
4
8
12
16
msec

When impulse reaches excitatory synaptic bouton, it causes release of a transmitter substance into synaptic cleft. This increases permeability of postsynaptic membrane to Na^+ and K^+. More Na^+ moves into postsynaptic cell than K^+ moves out, due to greater electrochemical gradient

At inhibitory synapse, transmitter substance released by an impulse increases permeability of the postsynaptic membrane to Cl^-. K^+ moves out of post-synaptic cell but no net flow of Cl^- occurs at resting membrane potential

Resultant net ionic current flow is in a direction that tends to depolarize postsynaptic cell. If depolarization reaches firing threshold, an impulse is generated in postsynaptic cell

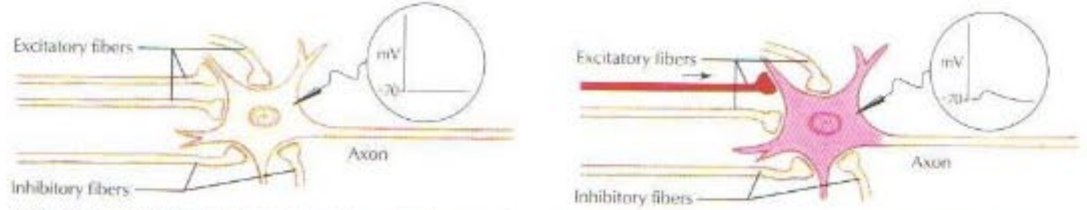
Resultant ionic current flow is in direction that tends to hyperpolarize postsynaptic cell. This makes depolarization by excitatory synapses more difficult—more depolarization is required to reach threshold

Current flow and potential change

Current flow and potential change

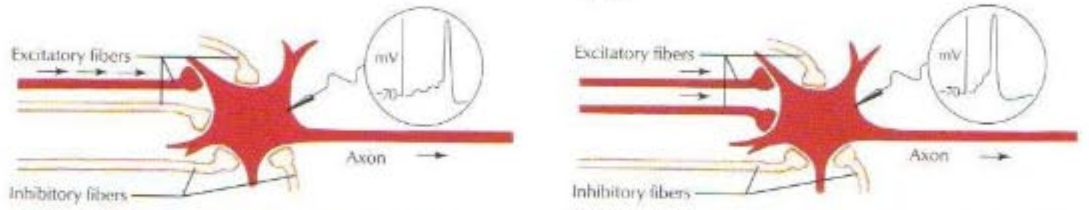
FIGURE 2.8 CHEMICAL SYNAPTIC TRANSMISSION

Chemical synaptic transmission between neurons may be excitatory or inhibitory. During excitation (left column), a net increase in the inward flow of Na^+ compared with the outward flow of K^+ results in a depolarizing potential change (excitatory postsynaptic potential [EPSP]) that drives the postsynaptic cell closer to its threshold for an action potential. During inhibition (right column), the opening of K^+ and Cl^- channels drives the membrane potential away from threshold (hyperpolarization) and decreases the probability that the neuron will reach threshold (inhibitory postsynaptic potential [IPSP]) for an action potential.


Excitatory fibers
mV
-70
Axon
Inhibitory fibers
Excitatory fibers
mV
-70
Axon
Inhibitory fibers

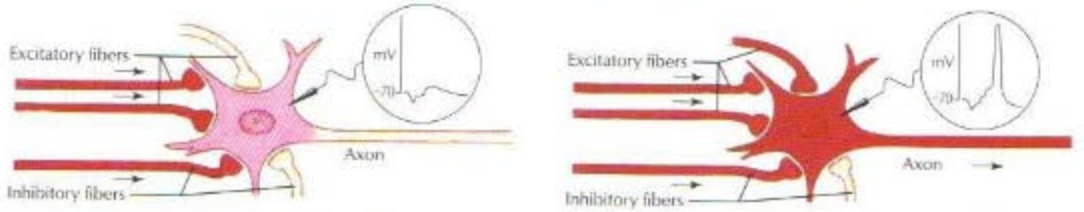
A. Resting state: motor nerve cell shown with synaptic boutons of excitatory and inhibitory nerve fibers ending close to it

B. Partial depolarization: impulse from one excitatory fiber has caused partial (below firing threshold) depolarization of motor neuron


Excitatory fibers
mV
-70
Axon
Inhibitory fibers
Excitatory fibers
mV
-70
Axon
Inhibitory fibers

C. Temporal excitatory summation: a series of impulses in one excitatory fiber together produce a suprathreshold depolarization that triggers an action potential

D. Spatial excitatory summation: impulses in two excitatory fibers cause two synaptic depolarizations that together reach firing threshold triggering an action potential


Excitatory fibers
mV
-70
Axon
Inhibitory fibers
Excitatory fibers
mV
-70
Axon
Inhibitory fibers

E. Spatial excitatory summation with inhibition: impulses from two excitatory fibers reach motor neuron but impulses from inhibitory fiber prevent depolarization from reaching threshold

E. (continued): motor neuron now receives additional excitatory impulses and reaches firing threshold despite a simultaneous inhibitory impulse; additional inhibitory impulses might still prevent firing

CHART 2.1 SUMMARY OF SOME NEUROTRANSMITTERS AND WHERE WITHIN THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM THEY ARE FOUND

Transmitter	Location
Acetylcholine	Neuromuscular junction, autonomic endings and ganglia, CNS
Biogenic amines	
Norepinephrine	Sympathetic endings, CNS
Dopamine	CNS
Serotonin	CNS, GI tract
Amino acids	
γ-Aminobutyric acid (GABA)	CNS
Glutamate	CNS
Purines	
Adenosine	CNS
Adenosine triphosphate (ATP)	CNS
Gas	
Nitric oxide	CNS, GI tract
Peptides	
β-Endorphins	CNS, GI tract
Enkephalins	CNS
Antidiuretic hormone	CNS (hypothalamus/posterior pituitary)
Pituitary-releasing hormones	CNS (hypothalamus/anterior pituitary)
Somatostatin	CNS, GI tract
Neuropeptide Y	CNS
Vasoactive intestinal peptide	CNS, GI tract

CNS, Central nervous system; *GI,* gastrointestinal.

FIGURE 2.9 TEMPORAL AND SPATIAL SUMMATION

Neurons receive multiple excitatory and inhibitory inputs. Temporal summation occurs when a series of subthreshold impulses in one excitatory fiber produces an action potential in the postsynaptic cell (panel C). Spatial summation occurs when subthreshold impulses from two or more different fibers trigger an action potential (panel D). Both temporal and spatial summation can be modulated by simultaneous inhibitory input (panel E). Inhibitory and excitatory neurons use a wide variety of neurotransmitters, some of which are summarized here.

Left lateral phantom view

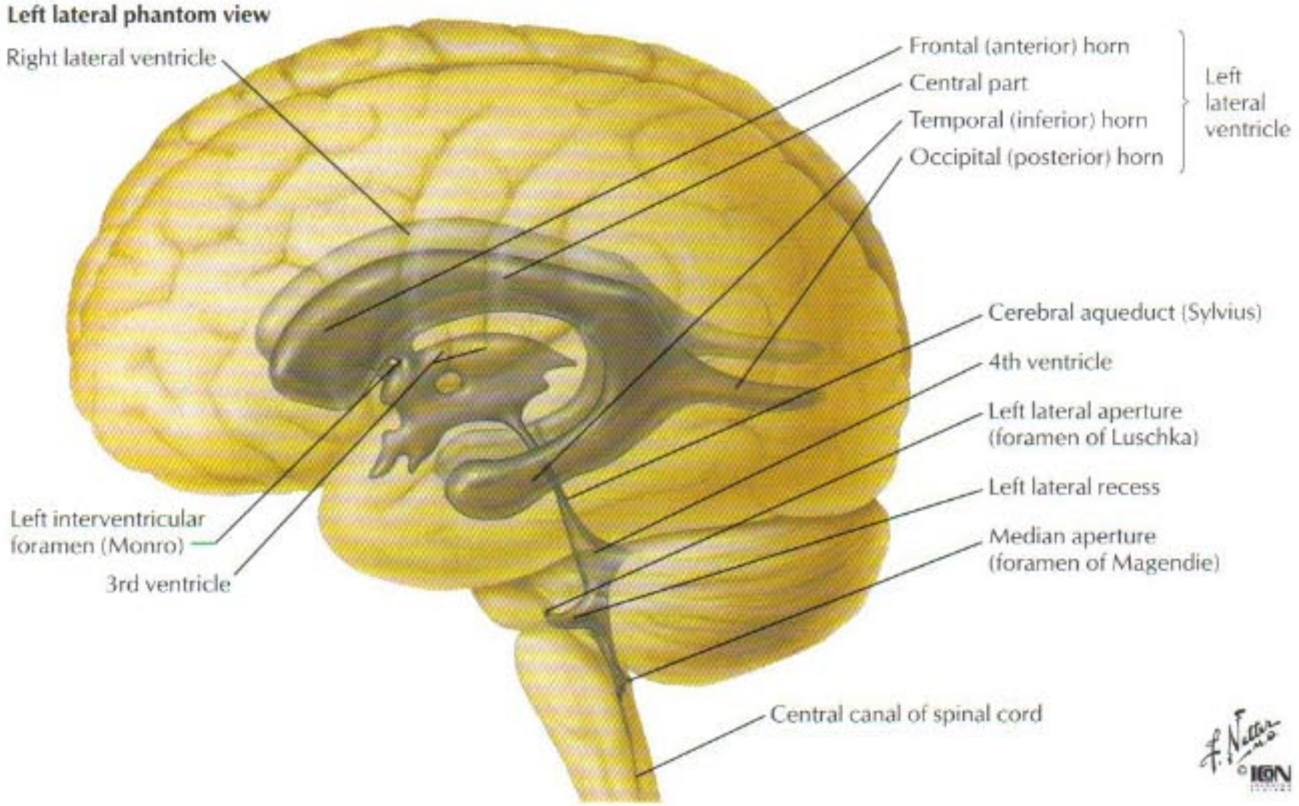

Right lateral ventricle
Frontal (anterior) horn
Central part
Temporal (inferior) horn
Occipital (posterior) horn
Left lateral ventricle
Cerebral aqueduct (Sylvius)
4th ventricle
Left lateral aperture (foramen of Luschka)
Left lateral recess
Median aperture (foramen of Magendie)
Left interventricular foramen (Monro)
3rd ventricle
Central canal of spinal cord

CHART 2.2 CSF COMPOSITION

	CSF	Blood Plasma
Na^+ (mEq/L)	140–145	135–147
K^+ (mEq/L)	3	3.5–5.0
Cl^- (mEq/L)	115–120	95–105
HCO_3^- (mEq/L)	20	22–28
Glucose (mg/dL)	50–75	70–110
Protein (g/dL)	0.05–0.07	6.0–7.8
pH	7.3	7.35–7.45

FIGURE 2.10 BRAIN VENTRICLES AND CSF COMPOSITION

CSF circulates through the four brain ventricles (two lateral ventricles and a third and fourth ventricle) and in the subarachnoid space surrounding the brain and spinal cord. The electrolyte composition of the CSF is regulated by the choroid plexus, which secretes the CSF. Importantly, the CSF has a lower [HCO_3^-] than plasma and therefore a lower pH. This allows small changes in blood P_{CO_2} to cause changes in CSF pH, which in turn regulates the rate of respiration (see Chapter 5).

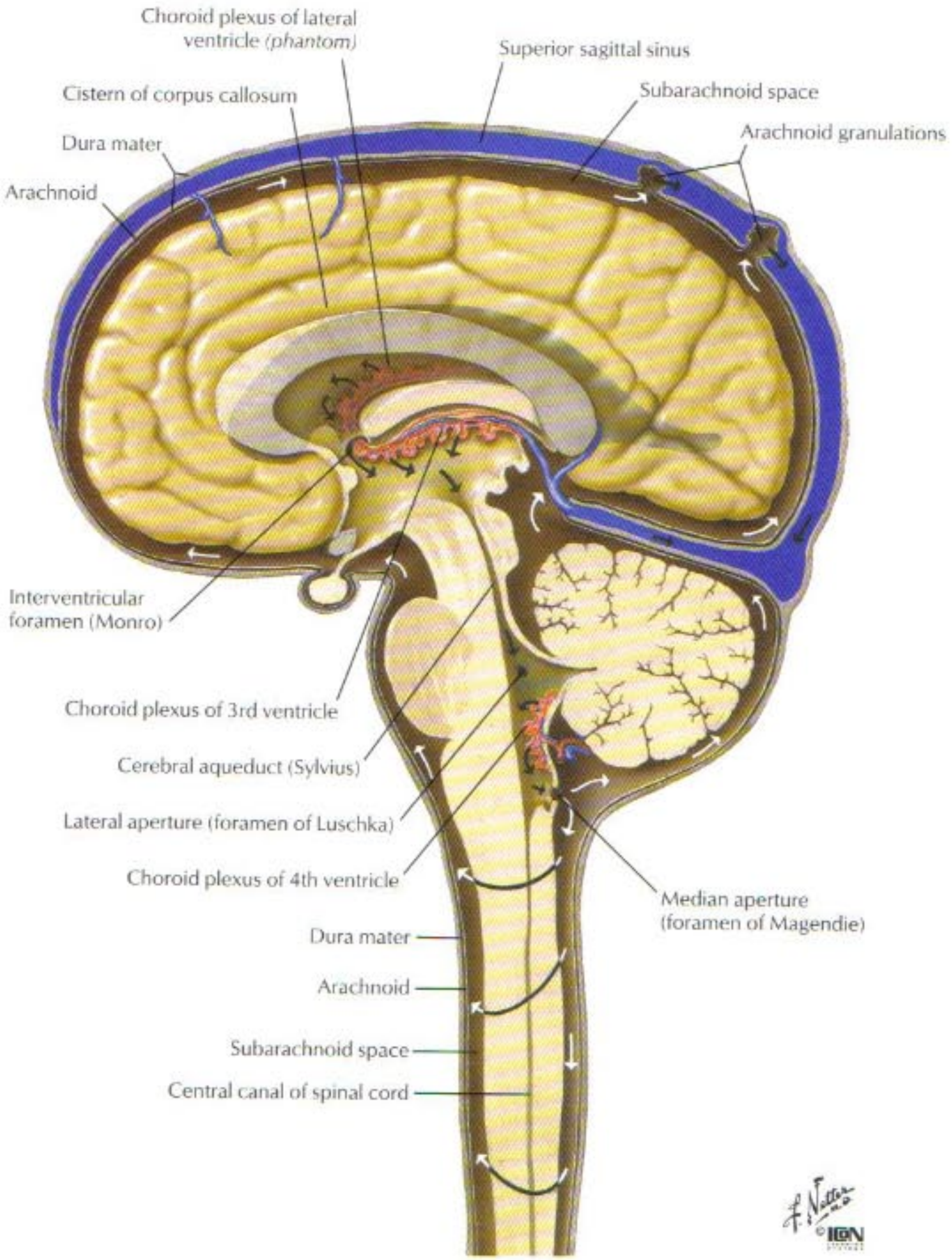

Choroid plexus of lateral ventricle (*phantom*)
Superior sagittal sinus
Cistern of corpus callosum
Subarachnoid space
Dura mater
Arachnoid granulations
Arachnoid
Interventricular foramen (Monro)
Choroid plexus of 3rd ventricle
Cerebral aqueduct (Sylvius)
Lateral aperture (foramen of Luschka)
Choroid plexus of 4th ventricle
Median aperture (foramen of Magendie)
Dura mater
Arachnoid
Subarachnoid space
Central canal of spinal cord

Figure 2.11 Circulation of Cerebrospinal Fluid

CSF circulates through the four brain ventricles (two lateral ventricles and a third and fourth ventricle) and in the subarachnoid space surrounding the brain and spinal cord. Most of the CSF is reabsorbed into the venous system through the arachnoid granulations and through the walls of the capillaries of the central nervous system and pia mater. The subarachnoid space normally contains about 150 ml of CSF and the choroid plexus produces about 500ml/day; hence, CSF turns over about three times every 24 hours.

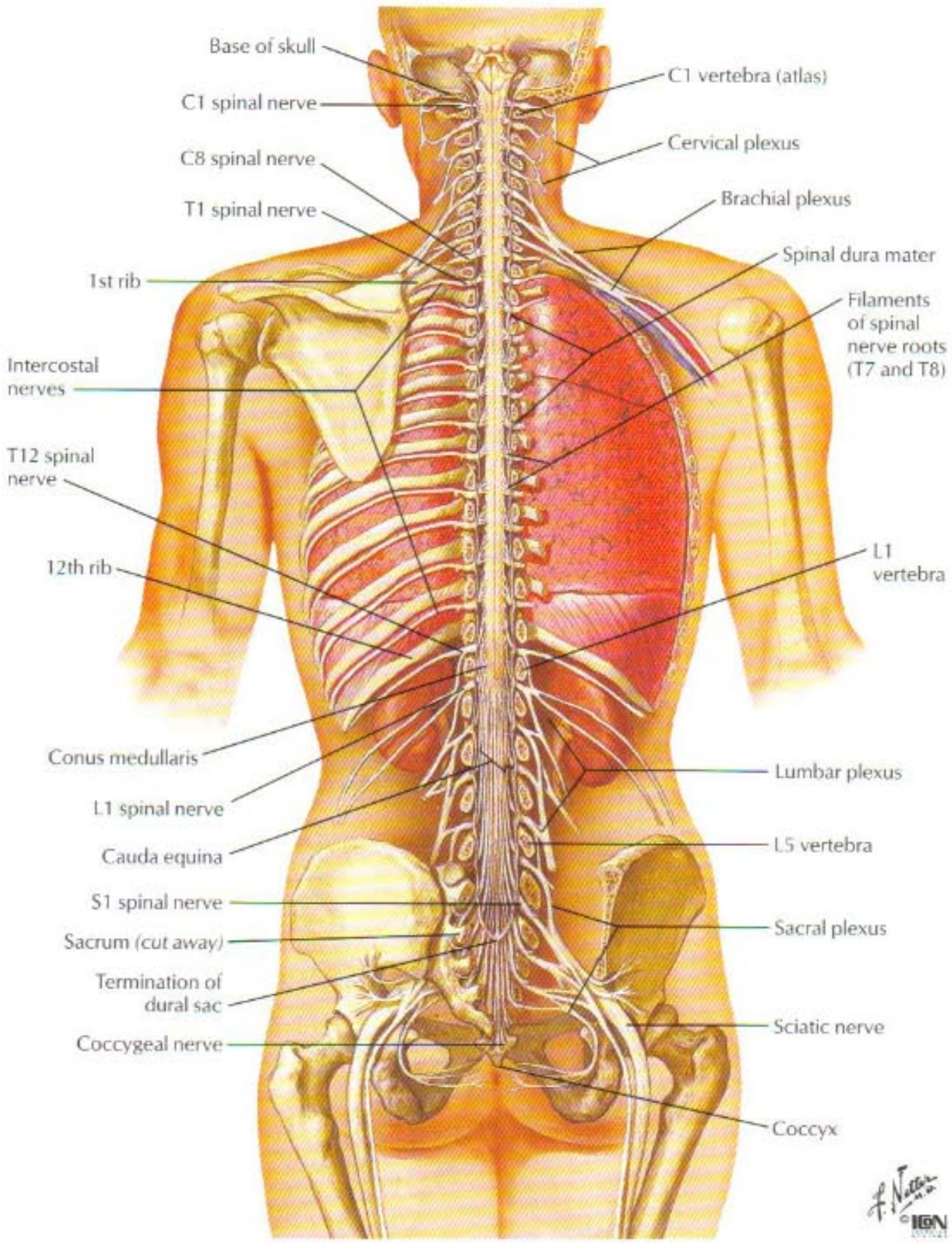

Base of skull
C1 spinal nerve
C8 spinal nerve
T1 spinal nerve
1st rib
Intercostal nerves
T12 spinal nerve
12th rib
Conus medullaris
L1 spinal nerve
Cauda equina
S1 spinal nerve
Sacrum *(cut away)*
Termination of dural sac
Coccygeal nerve
C1 vertebra (atlas)
Cervical plexus
Brachial plexus
Spinal dura mater
Filaments of spinal nerve roots (T7 and T8)
L1 vertebra
Lumbar plexus
L5 vertebra
Sacral plexus
Sciatic nerve
Coccyx

FIGURE 2.12 SPINAL CORD AND VENTRAL RAMI IN SITU

The spinal cord gives rise to 31 pairs of spinal nerves that distribute segmentally to the body. These nerves are organized into plexuses that distribute to the neck (cervical plexus), upper limb (brachial plexus), and pelvis and lower limb (lumbosacral plexus). Motor fibers of these spinal nerves innervate skeletal muscle, and sensory fibers convey information back to the central nervous system from the skin, skeletal muscles, and joints.

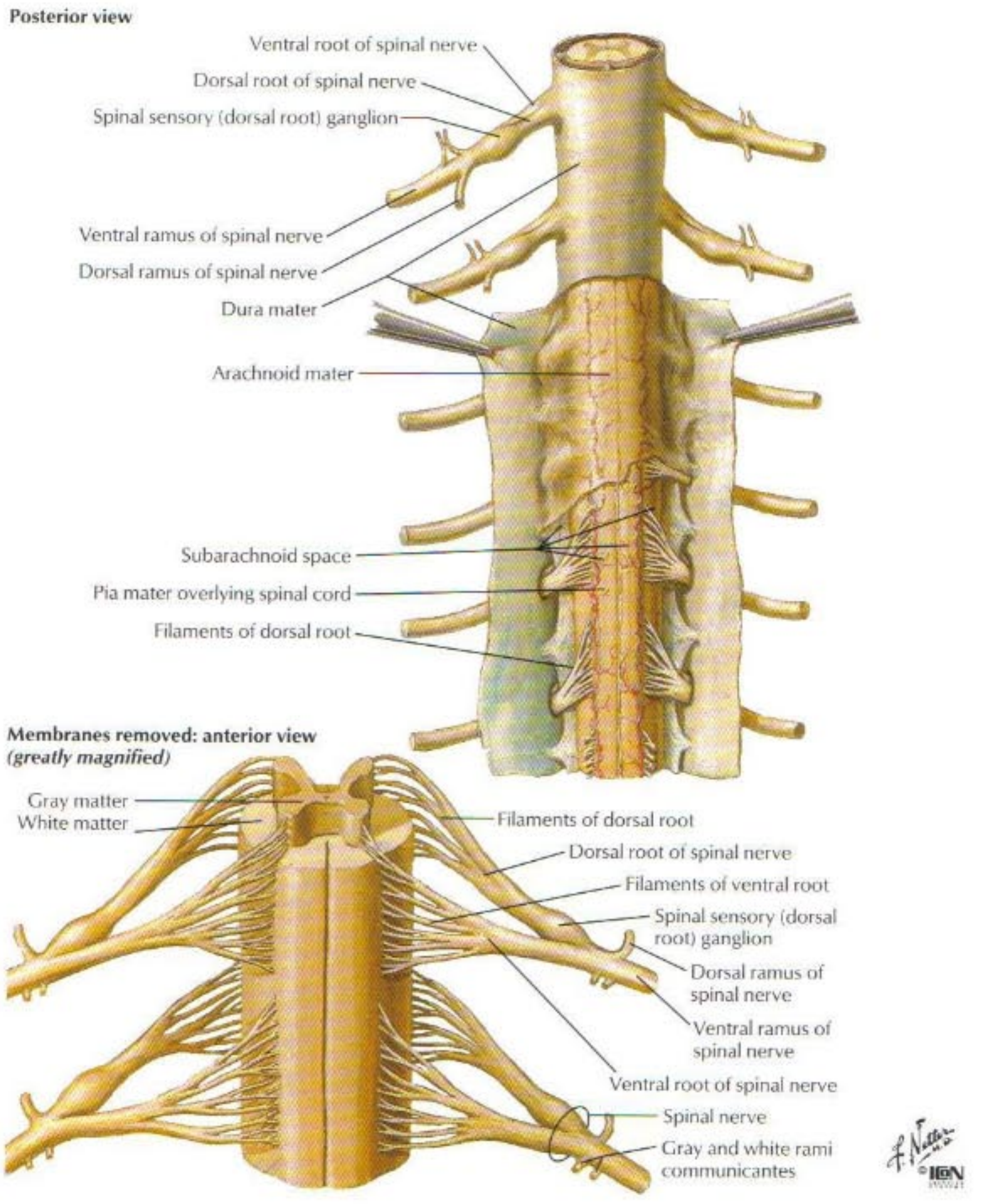

Posterior view
Ventral root of spinal nerve
Dorsal root of spinal nerve
Spinal sensory (dorsal root) ganglion
Ventral ramus of spinal nerve
Dorsal ramus of spinal nerve
Dura mater
Arachnoid mater
Subarachnoid space
Pia mater overlying spinal cord
Filaments of dorsal root
Membranes removed: anterior view
(greatly magnified)
Gray matter
White matter
Filaments of dorsal root
Dorsal root of spinal nerve
Filaments of ventral root
Spinal sensory (dorsal root) ganglion
Dorsal ramus of spinal nerve
Ventral ramus of spinal nerve
Ventral root of spinal nerve
Spinal nerve
Gray and white rami communicantes

FIGURE 2.13 **SPINAL MEMBRANES AND NERVE ROOTS**

The spinal cord gives rise to 31 pairs of spinal nerves that distribute segmentally to the body. Motor fibers of these spinal nerves innervate skeletal muscle, and sensory fibers convey information back to the central nervous system from the skin, skeletal muscles, and joints.

The spinal cord is ensheathed in three meningeal coverings: the outer, tough dura mater; the arachnoid mater; and the pia mater, which intimately ensheaths the cord itself. CSF bathes the cord and is found in the subarachnoid space.

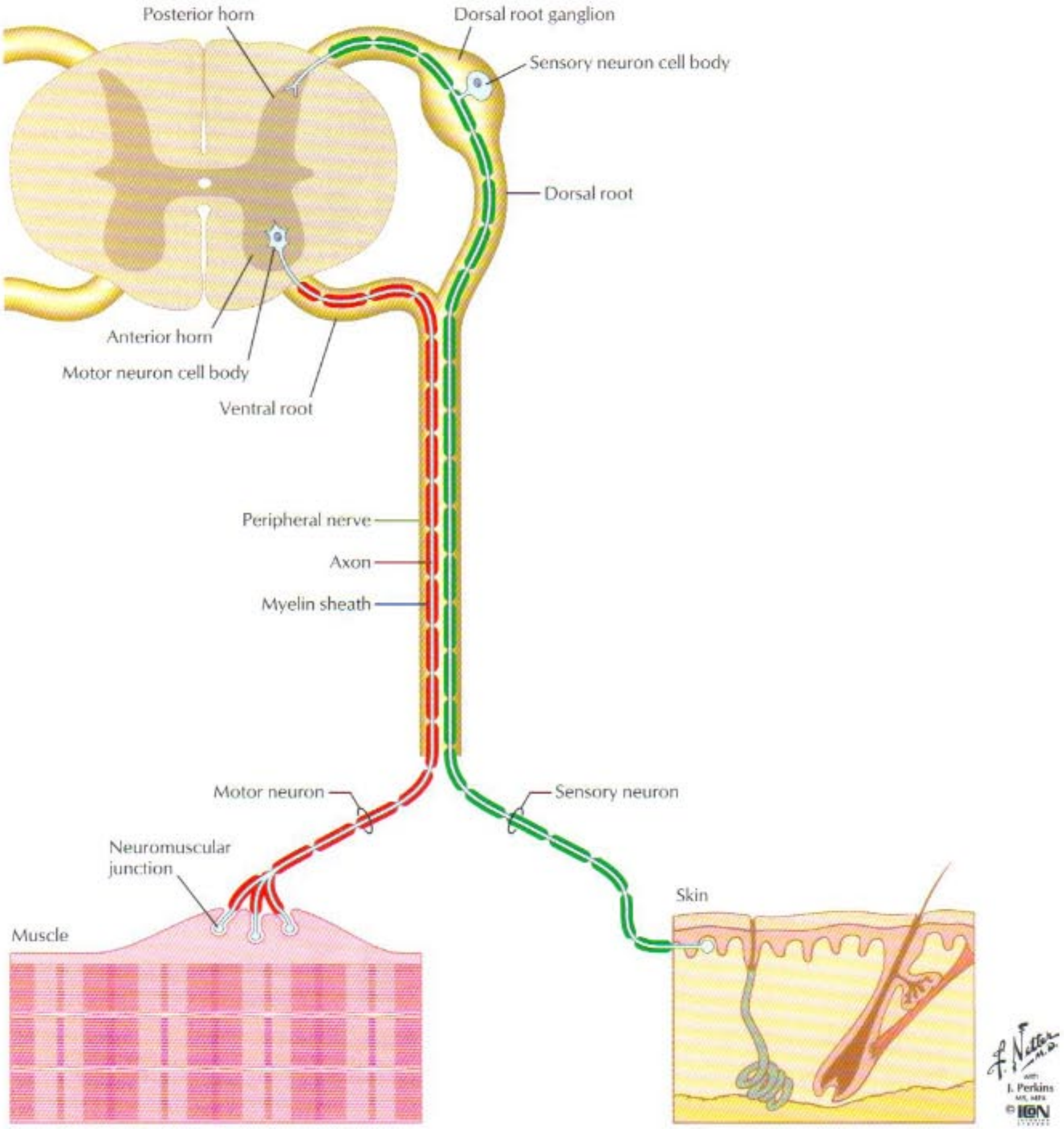

Posterior horn
Dorsal root ganglion
Sensory neuron cell body
Dorsal root
Anterior horn
Motor neuron cell body
Ventral root
Peripheral nerve
Axon
Myelin sheath
Motor neuron
Sensory neuron
Neuromuscular junction
Muscle
Skin
J. Perkins
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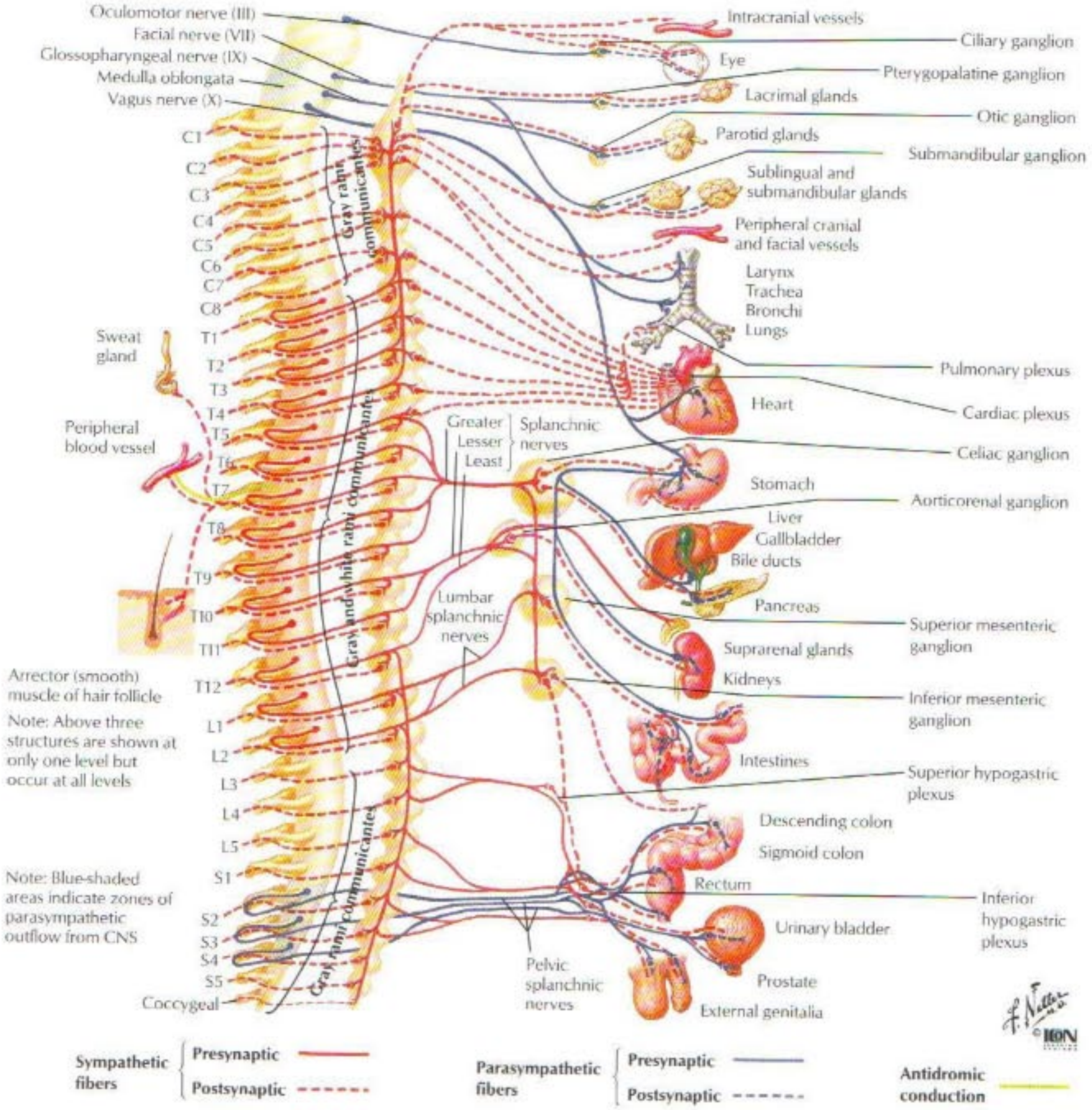
FIGURE 2.14 PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) consists of all of the neural elements outside of the CNS (brain and spinal cord) and provides the connections between the CNS and all other body organ systems. The PNS consists of somatic and autonomic components. The somatic component innervates skeletal muscle and skin and is shown here (see Figure 2.15 for the autonomic nervous system). The somatic component of the peripheral nerves contains both motor and sensory axons. Cell bodies of the motor neurons are found in the anterior horn gray matter, whereas the cell bodies of sensory neurons are located in the dorsal root ganglia.


Oculomotor nerve (III)
Facial nerve (VII)
Glossopharyngeal nerve (IX)
Medulla oblongata
Vagus nerve (X)
C1
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Coccygeal
Gray rami communicantes
Gray and white rami communicantes
Sweat gland
Peripheral blood vessel
Arrector (smooth) muscle of hair follicle
Note: Above three structures are shown at only one level but occur at all levels
Note: Blue-shaded areas indicate zones of parasympathetic outflow from CNS
Intracranial vessels
Ciliary ganglion
Eye
Pterygopalatine ganglion
Lacrimal glands
Otic ganglion
Parotid glands
Submandibular ganglion
Sublingual and submandibular glands
Peripheral cranial and facial vessels
Larynx
Trachea
Bronchi
Lungs
Pulmonary plexus
Heart
Cardiac plexus
Greater
Lesser
Least
Splanchnic nerves
Celiac ganglion
Stomach
Aorticorenal ganglion
Liver
Gallbladder
Bile ducts
Pancreas
Lumbar splanchnic nerves
Superior mesenteric ganglion
Suprarenal glands
Kidneys
Inferior mesenteric ganglion
Intestines
Superior hypogastric plexus
Descending colon
Sigmoid colon
Rectum
Inferior hypogastric plexus
Urinary bladder
Pelvic splanchnic nerves
Prostate
External genitalia
F. Netter
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Sympathetic fibers
Presynaptic
Postsynaptic
Parasympathetic fibers
Presynaptic
Postsynaptic
Antidromic conduction

FIGURE 2.15 AUTONOMIC NERVOUS SYSTEM: SCHEMA

The autonomic nervous system is composed of two divisions: the parasympathetic division derived from four of the cranial nerves (CN III, VII, IX, and X) and the S2-S4 sacral spinal cord levels, and the sympathetic division associated with the thoracic and upper lumbar spinal cord levels (T1-L2). The autonomic nervous system is a two-neuron chain, with the preganglionic neuron arising from the central nervous system and synapsing on a postganglionic neuron located in a peripheral autonomic ganglion. Postganglionic axons of the autonomic nervous system innervate smooth muscle, cardiac muscle, and glands. Basically, the sympathetic division mobilizes our body ("fight or flight") while the parasympathetic division regulates digestive and homeostatic functions. Normally, both divisions work in concert to regulate visceral activity (respiration, cardiovascular function, digestion, and associated glandular activity).

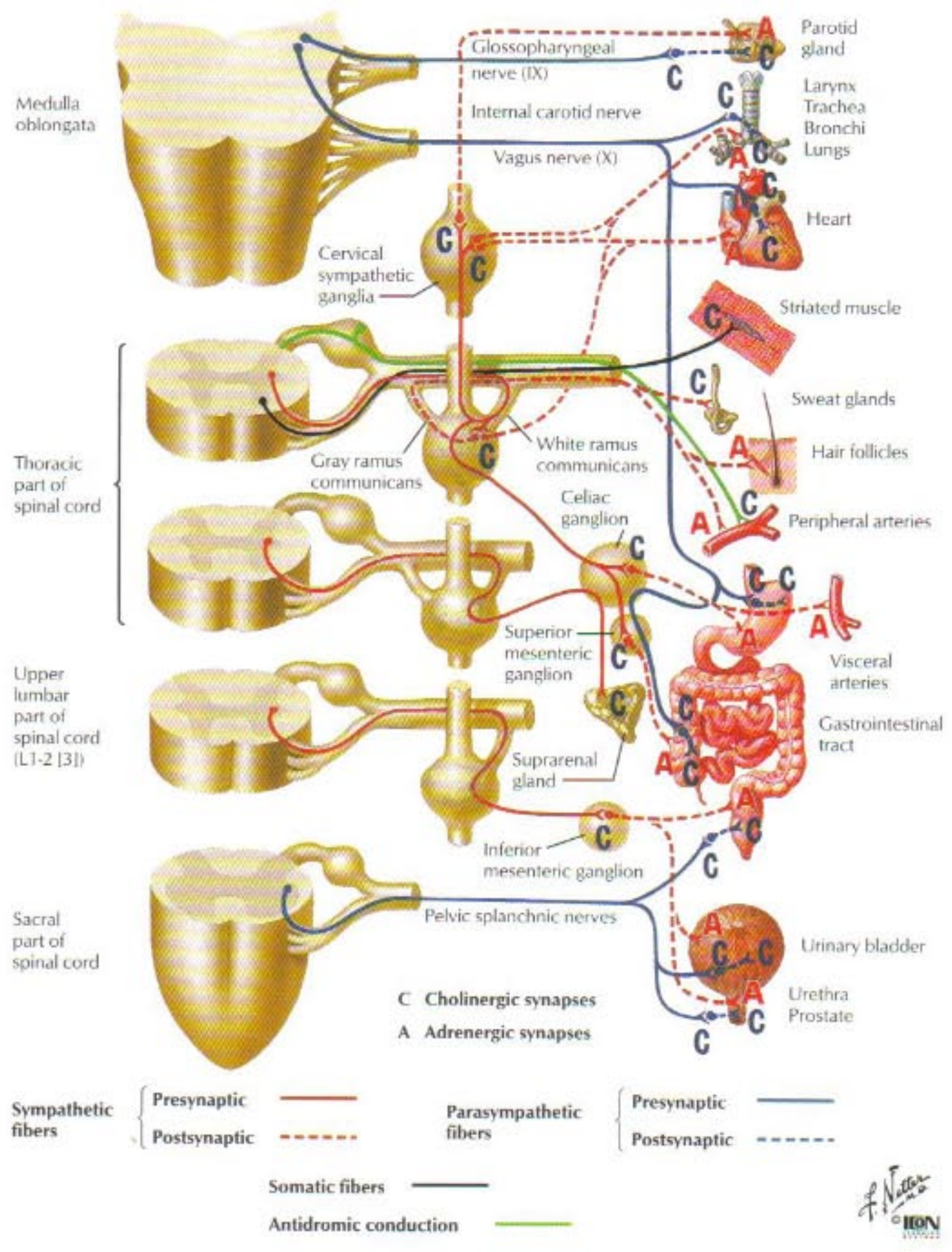
Medulla oblongata
Glossopharyngeal nerve (IX)
Internal carotid nerve
Vagus nerve (X)
Parotid gland
Larynx
Trachea
Bronchi
Lungs
Heart
Cervical sympathetic ganglia
Striated muscle
Thoracic part of spinal cord
Sweat glands
Hair follicles
Gray ramus communicans
White ramus communicans
Celiac ganglion
Peripheral arteries
Superior mesenteric ganglion
Visceral arteries
Upper lumbar part of spinal cord (L1-2 [3])
Gastrointestinal tract
Suprarenal gland
Inferior mesenteric ganglion
Sacral part of spinal cord
Pelvic splanchnic nerves
Urinary bladder
Urethra
Prostate
C Cholinergic synapses
A Adrenergic synapses
Sympathetic fibers
Presynaptic
Postsynaptic
Parasympathetic fibers
Presynaptic
Postsynaptic
Somatic fibers
Antidromic conduction
F. Netter
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FIGURE 2.16 CHOLINERGIC AND ADRENERGIC SYNAPSES: SCHEMA

The autonomic nervous system (ANS) is a two-neuron chain, with the preganglionic neuron arising from the central nervous system and synapsing on a postganglionic neuron located in a peripheral autonomic ganglion. Acetylcholine is the neurotransmitter in both the sympathetic and parasympathetic ganglia. The parasympathetic division of the ANS releases acetylcholine at its postganglionic synapses and is characterized as having cholinergic (C) effects, whereas the sympathetic division releases predominantly noradrenaline (norepinephrine) at its postganglionic synapses, causing adrenergic (A) effects (except on sweat glands, where acetylcholine is released). Although acetylcholine and noradrenaline are the chief transmitter substances, other neuroactive peptides often are colocalized with them and include such substances as gamma-aminobutyric acid (GABA), substance P, enkephalins, histamine, glutamic acid, neuropeptide Y, and others.

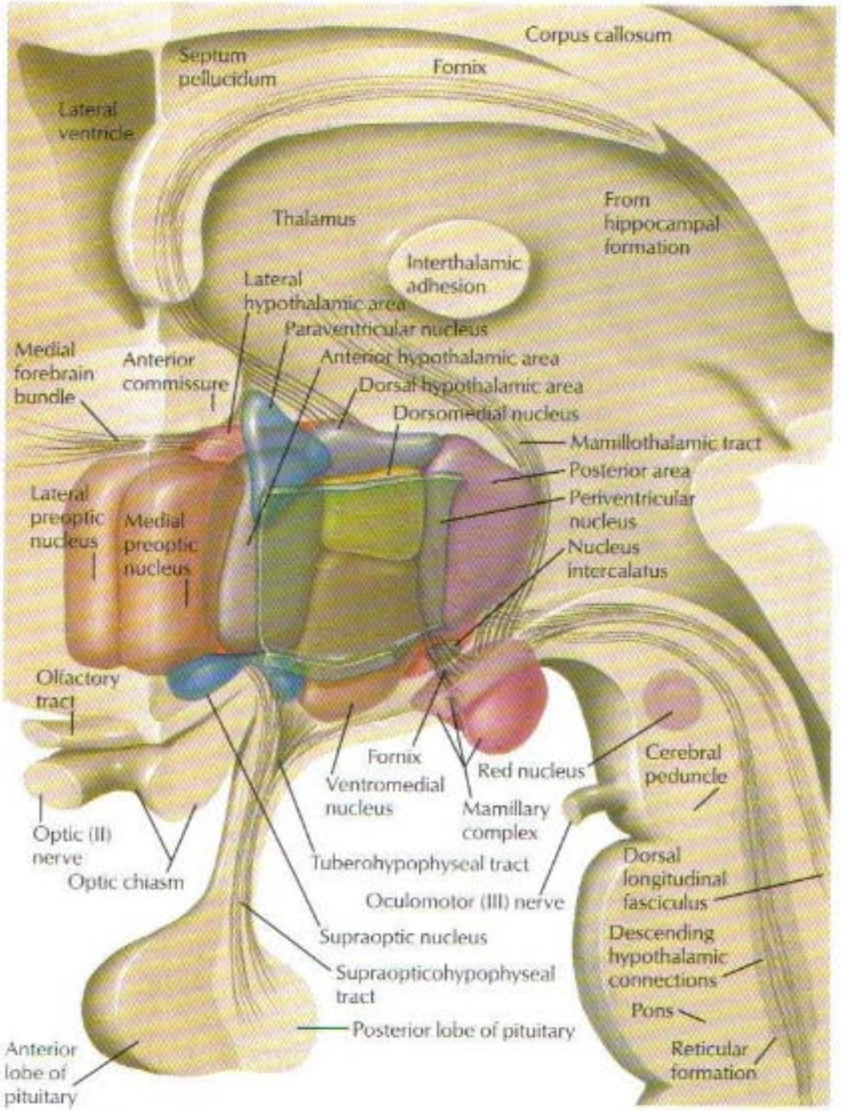
Septum pellucidum
Corpus callosum
Fornix
Lateral ventricle
Thalamus
From hippocampal formation
Interthalamic adhesion
Lateral hypothalamic area
Paraventricular nucleus
Medial forebrain bundle
Anterior commissure
Anterior hypothalamic area
Dorsal hypothalamic area
Dorsomedial nucleus
Mamillothalamic tract
Posterior area
Periventricular nucleus
Nucleus intercalatus
Lateral preoptic nucleus
Medial preoptic nucleus
Olfactory tract
Fornix
Ventromedial nucleus
Red nucleus
Mamillary complex
Cerebral peduncle
Optic (II) nerve
Optic chiasm
Tuberohypophyseal tract
Oculomotor (III) nerve
Dorsal longitudinal fasciculus
Supraoptic nucleus
Supraopticohypophyseal tract
Descending hypothalamic connections
Pons
Posterior lobe of pituitary
Anterior lobe of pituitary
Reticular formation
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CHART 2.3 MAJOR FUNCTIONS OF THE HYPOTHALAMUS

Hypothalamic Area	Major Functions*
Preoptic and anterior	Heat loss center: cutaneous vasodilation and sweating
Posterior	Heat conservation center: cutaneous vasoconstriction and shivering
Lateral	Feeding center: eating behavior
Ventromedial	Satiety center: inhibits eating behavior
Supraoptic (subfornical organ and organum vasculosum)	ADH and oxytocin secretion (sensation of thirst)
Paraventricular	ADH and oxytocin secretion
Periventricular	Releasing hormones for the anterior pituitary

*Stimulation of the center causes the responses listed.

FIGURE 2.17 SCHEMATIC RECONSTRUCTION OF THE HYPOTHALAMUS

The hypothalamus, part of the diencephalon, controls a number of important homeostatic systems within the body, including temperature regulation, food intake, water intake, many of the endocrine systems (see Chapter 8), motivation, and emotional behavior. It receives inputs from the reticular formation (sleep/wake cycle information), the thalamus (pain), the limbic system (emotion, fear, anger, smell), the medulla oblongata (blood pressure and heart rate), and the optic system, and it integrates these inputs for regulation of the functions listed.

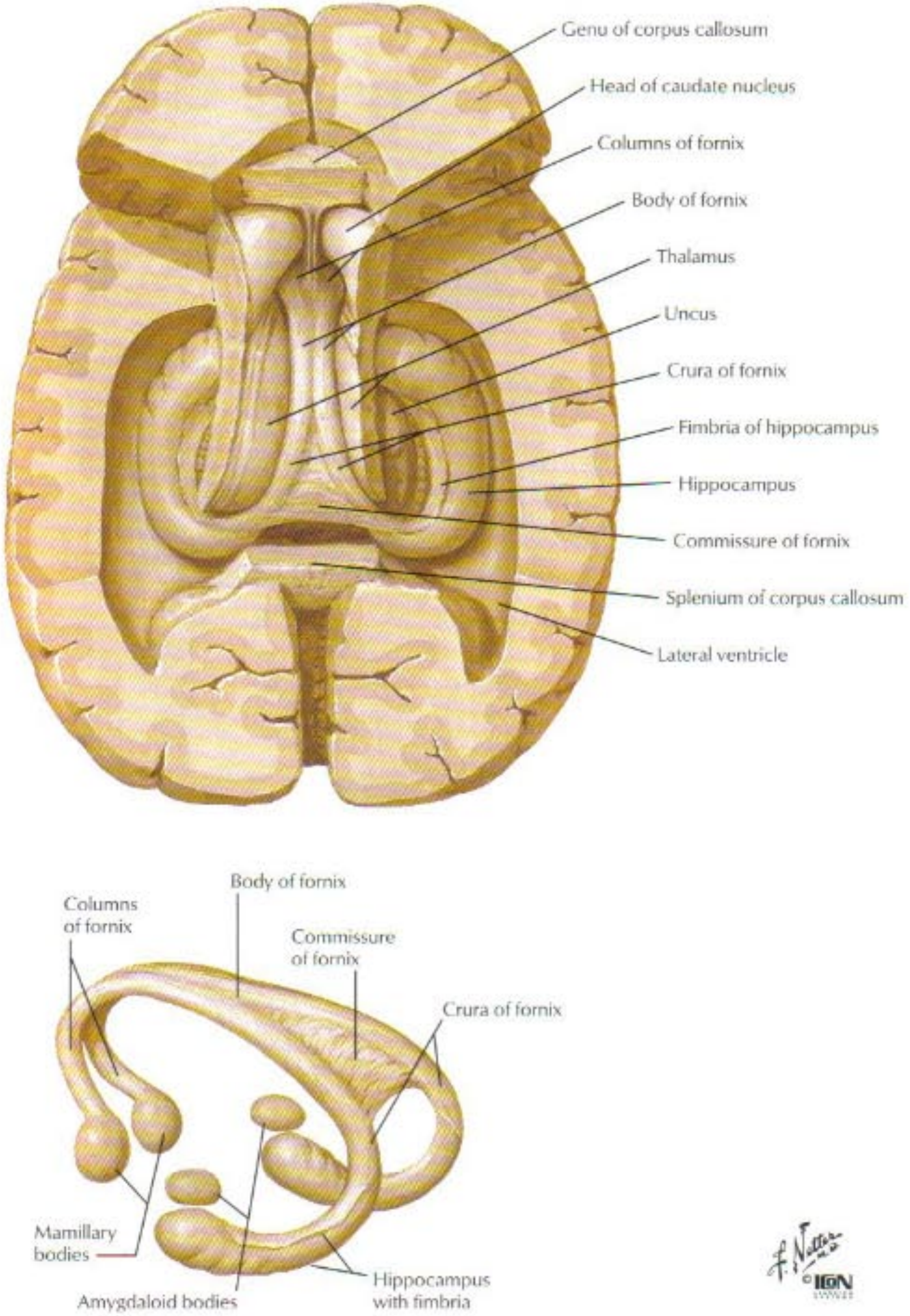

Genu of corpus callosum
Head of caudate nucleus
Columns of fornix
Body of fornix
Thalamus
Uncus
Crura of fornix
Fimbria of hippocampus
Hippocampus
Commissure of fornix
Splenium of corpus callosum
Lateral ventricle
Body of fornix
Columns of fornix
Commissure of fornix
Crura of fornix
Mamillary bodies
Amygdaloid bodies
Hippocampus with fimbria

Figure 2.18 Hippocampus and Fornix

The limbic system includes the hypothalamus and a collection of interconnected structures in the telencephalon (cingulate, parahippocampal, and subcallosal gyri), as well as the amygdala and hippocampal formation. The limbic system functions in linking emotion and motivation (amygdala), learning and memory (hippocampal formation), and sexual behavior (hypothalamus).

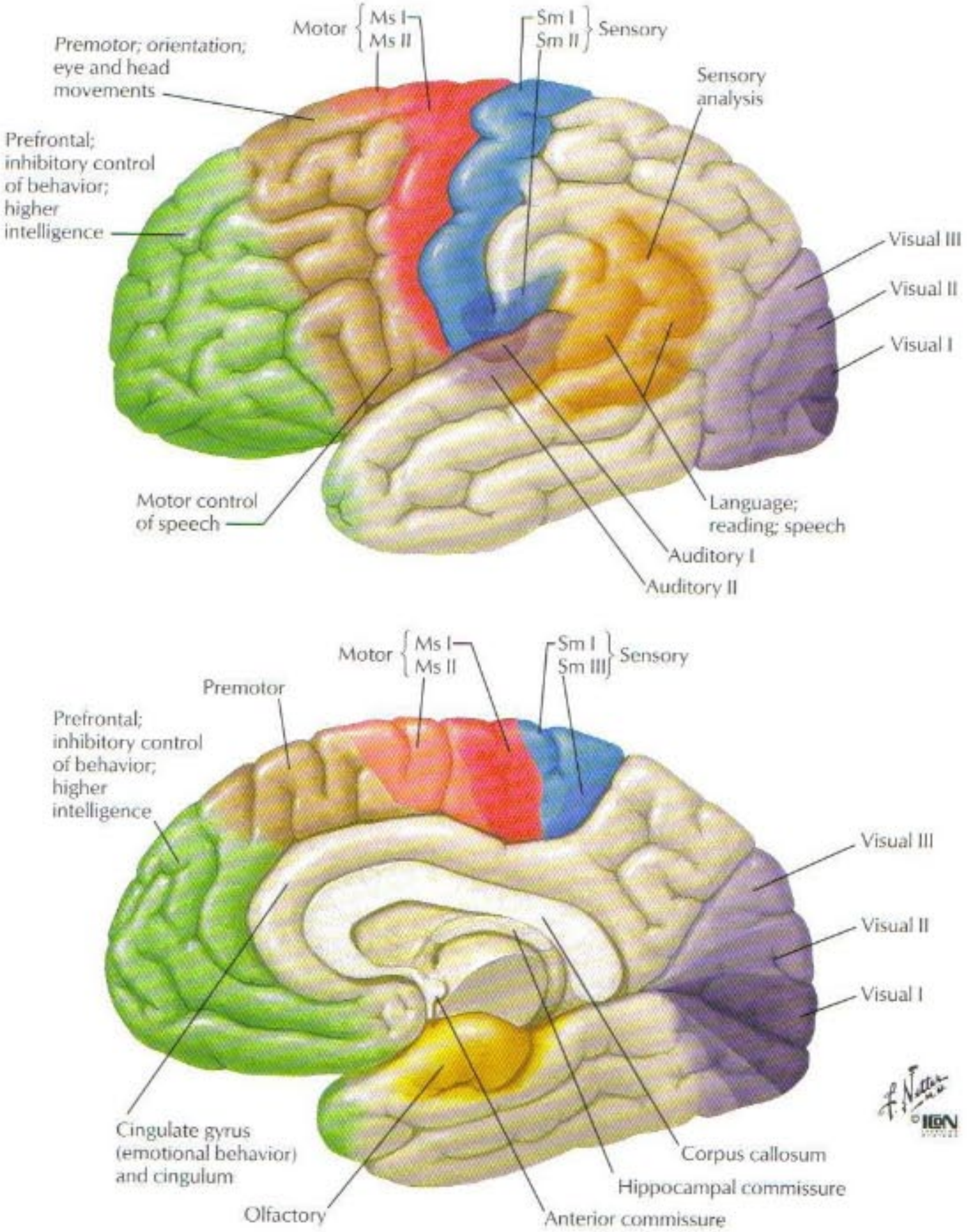
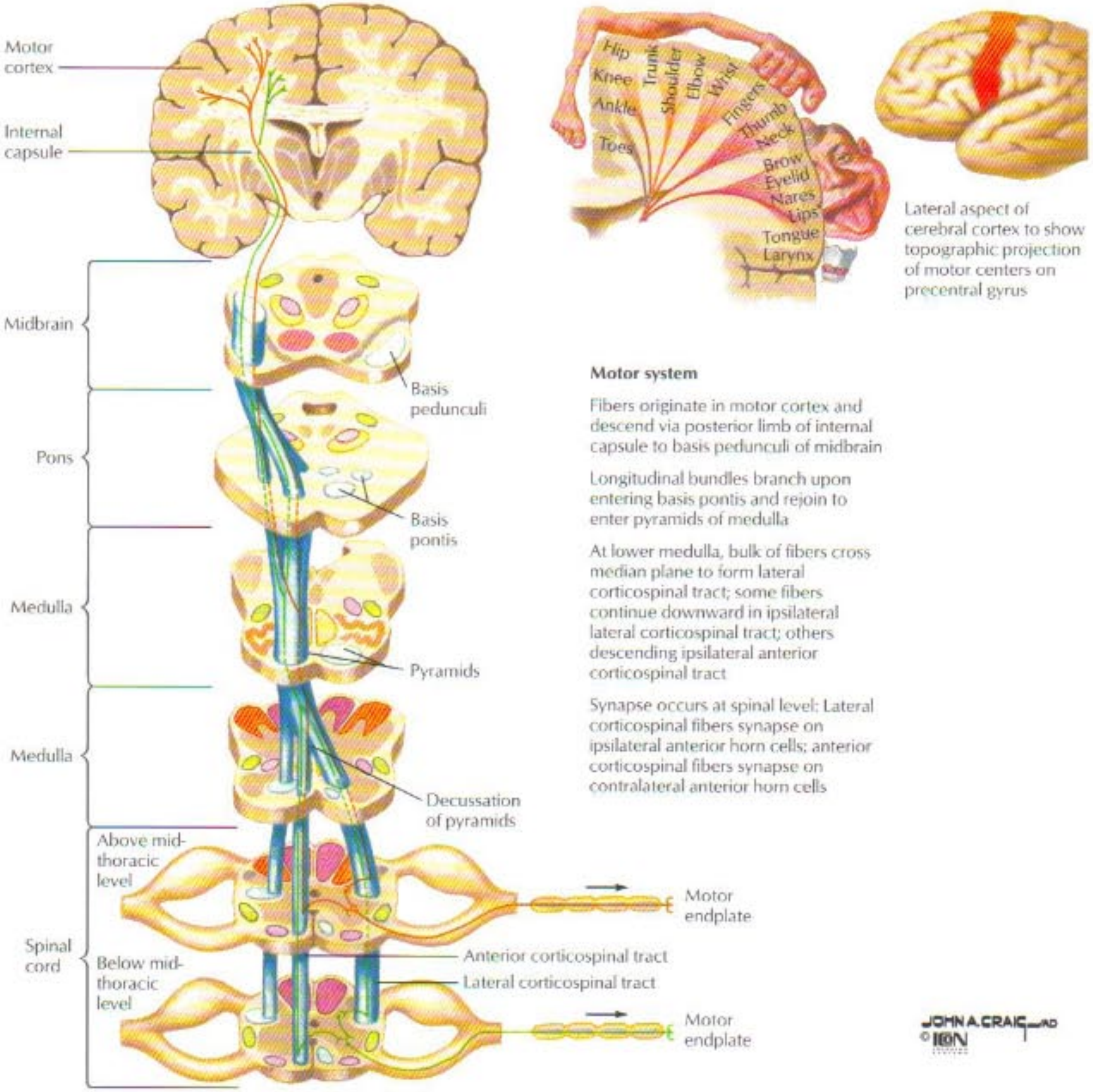

Motor
Ms I
Ms II
Sm I
Sm II
Sensory
Premotor; orientation; eye and head movements
Prefrontal; inhibitory control of behavior; higher intelligence
Sensory analysis
Visual III
Visual II
Visual I
Motor control of speech
Language; reading; speech
Auditory I
Auditory II
Motor
Ms I
Ms II
Sm I
Sm III
Sensory
Premotor
Prefrontal; inhibitory control of behavior; higher intelligence
Visual III
Visual II
Visual I
Cingulate gyrus (emotional behavior) and cingulum
Olfactory
Corpus callosum
Hippocampal commissure
Anterior commissure

FIGURE 2.19 CEREBRAL CORTEX: LOCALIZATION OF FUNCTION AND ASSOCIATION PATHWAYS

The cerebral cortex is organized into functional regions. In addition to specific areas devoted to sensory and motor functions, there are areas that integrate information from multiple sources. The cerebral cortex participates in advanced intellectual functions, including aspects of memory storage and recall, language, higher cognitive functions, conscious perception, sensory integration, and planning/execution of complex motor activity. General cortical areas associated with these functions are illustrated.


Motor cortex
Internal capsule
Midbrain
Pons
Medulla
Medulla
Spinal cord
Above mid-thoracic level
Below mid-thoracic level
Basis pedunculi
Basis pontis
Pyramids
Decussation of pyramids
Motor endplate
Anterior corticospinal tract
Lateral corticospinal tract
Motor endplate
Hip
Trunk
Shoulder
Elbow
Wrist
Knee
Ankle
Toes
Fingers
Thumb
Neck
Brow
Eyelid
Nares
Lips
Tongue
Larynx
JOHN A.CRAIG_AD
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Lateral aspect of cerebral cortex to show topographic projection of motor centers on precentral gyrus

Motor system

Fibers originate in motor cortex and descend via posterior limb of internal capsule to basis pedunculi of midbrain

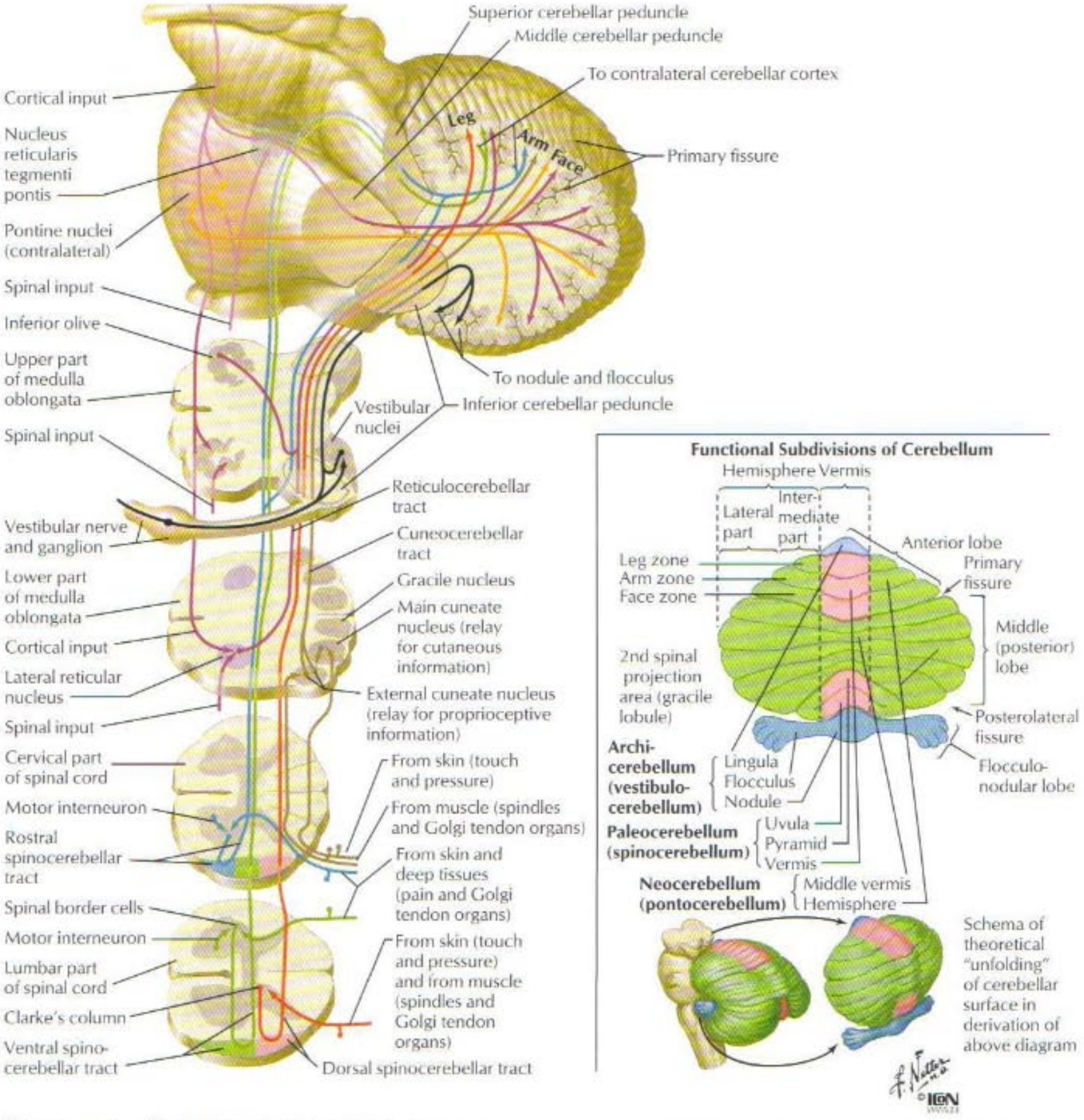
Longitudinal bundles branch upon entering basis pontis and rejoin to enter pyramids of medulla

At lower medulla, bulk of fibers cross median plane to form lateral corticospinal tract; some fibers continue downward in ipsilateral lateral corticospinal tract; others descending ipsilateral anterior corticospinal tract

Synapse occurs at spinal level: Lateral corticospinal fibers synapse on ipsilateral anterior horn cells; anterior corticospinal fibers synapse on contralateral anterior horn cells

FIGURE 2.20 CORTICOSPINAL TRACTS

The corticospinal, or pyramidal, tract is the major motor tract that controls voluntary movement of the skeletal muscles, especially skilled movements of distal muscles of the limbs. All structures from the cerebral cortex to the anterior horn cells in the spinal cord constitute the upper portion of the system (upper motor neuron). The anterior horn cells and their associated axons constitute the lower portion of the system (lower motor neuron).



Functional Subdivisions of Cerebellum

Schema of theoretical "unfolding" of cerebellar surface in derivation of above diagram

Superior cerebellar peduncle
Middle cerebellar peduncle
To contralateral cerebellar cortex
Cortical input
Nucleus reticularis tegmenti pontis
Leg
Arm
Face
Primary fissure
Pontine nuclei (contralateral)
Spinal input
Inferior olive
Upper part of medulla oblongata
To nodule and flocculus
Vestibular nuclei
Inferior cerebellar peduncle
Spinal input
Reticulocerebellar tract
Vestibular nerve and ganglion
Cuneocerebellar tract
Lower part of medulla oblongata
Gracile nucleus
Main cuneate nucleus (relay for cutaneous information)
Cortical input
Lateral reticular nucleus
External cuneate nucleus (relay for proprioceptive information)
Spinal input
Cervical part of spinal cord
From skin (touch and pressure)
Motor interneuron
From muscle (spindles and Golgi tendon organs)
Rostral spinocerebellar tract
From skin and deep tissues (pain and Golgi tendon organs)
Spinal border cells
Motor interneuron
From skin (touch and pressure) and from muscle (spindles and Golgi tendon organs)
Lumbar part of spinal cord
Clarke's column
Ventral spinocerebellar tract
Dorsal spinocerebellar tract
Hemisphere
Vermis
Lateral part
Intermediate part
Anterior lobe
Primary fissure
Leg zone
Arm zone
Face zone
Middle (posterior) lobe
2nd spinal projection area (gracile lobule)
Posterolateral fissure
Archicerebellum (vestibulocerebellum)
Lingula
Flocculus
Nodule
Flocculonodular lobe
Paleocerebellum (spinocerebellum)
Uvula
Pyramid
Vermis
Neocerebellum (pontocerebellum)
Middle vermis
Hemisphere
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Figure 2.21 Cerebellar Afferent Pathways

The cerebellum plays an important role in coordinating movement. It receives sensory information and then influences descending motor pathways to produce fine, smooth, and coordinated motion. The cerebellum is divided into three general areas: archicerebellum (also called vestibulocerebellum) paleocerebellum (also called spinocerebellum) and the neocerebellum (also called the cerebrocerebellum). The archicerebellum is primarily involved in controlling posture and balance, as well as the movement of the head and eyes. It receives afferent signals from the vestibular apparatus and then sends efferent fibers to the appropriate descending motor pathways. The paleocerebellum primarily controls movement of the proximal portions of the limbs. It receives sensory information on limb position and muscle tone and then modifies and coordinates these movements through efferent pathways to the appropriate descending motor pathways. The neocerebellum is the largest portion of the cerebellum, and it coordinates the movement of the distal portions of the limbs. It receives input from the cerebral cortex and thus helps in the planning of motor activity (e.g., seeing a pencil and then planning and executing the movement of the arm and hand to pick it up).

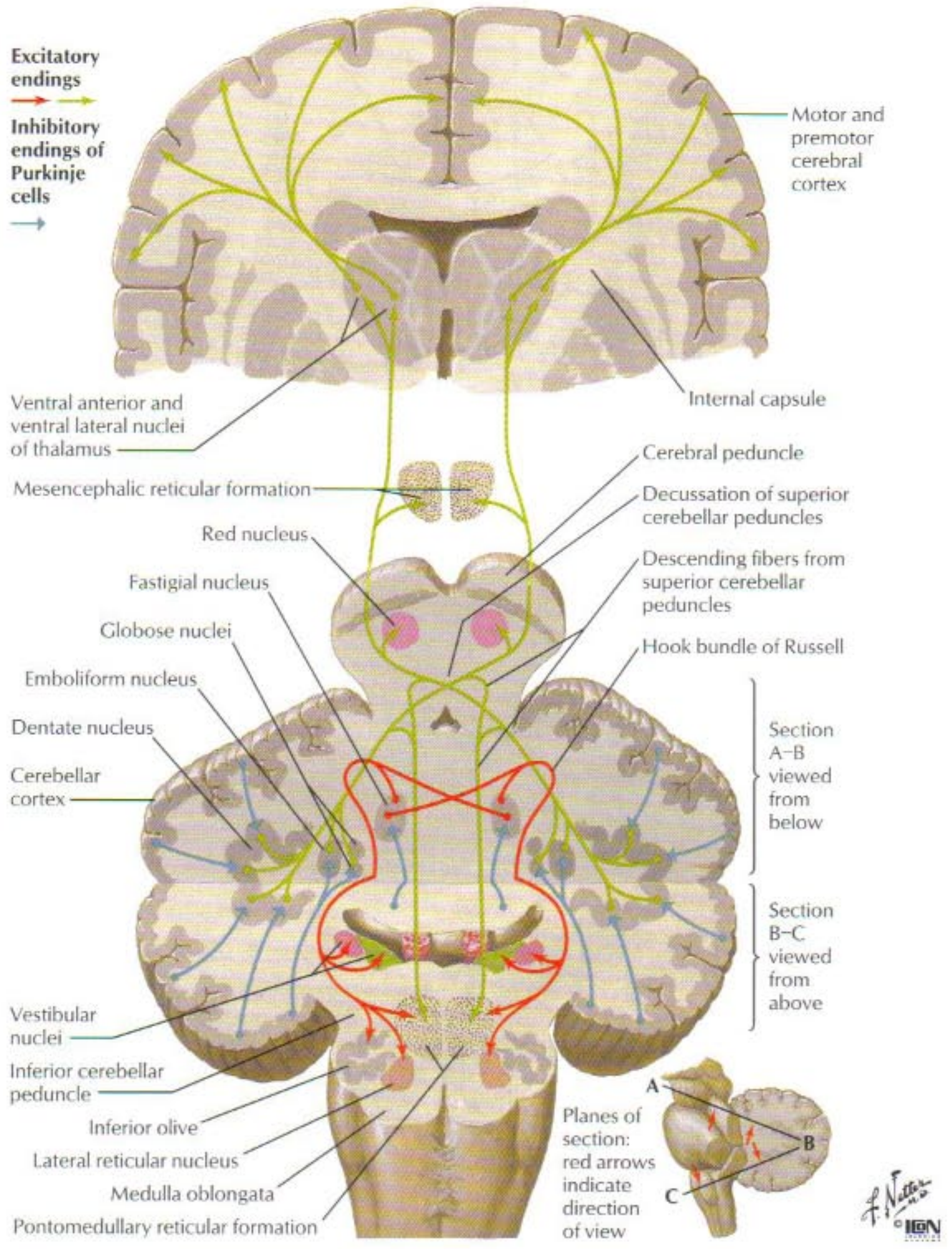
Excitatory endings
Inhibitory endings of Purkinje cells
Motor and premotor cerebral cortex
Internal capsule
Ventral anterior and ventral lateral nuclei of thalamus
Cerebral peduncle
Mesencephalic reticular formation
Decussation of superior cerebellar peduncles
Red nucleus
Descending fibers from superior cerebellar peduncles
Fastigial nucleus
Globose nuclei
Hook bundle of Russell
Emboliform nucleus
Dentate nucleus
Section A–B viewed from below
Cerebellar cortex
Section B–C viewed from above
Vestibular nuclei
Inferior cerebellar peduncle
Inferior olive
Lateral reticular nucleus
Medulla oblongata
Pontomedullary reticular formation
Planes of section: red arrows indicate direction of view
A
B
C

FIGURE 2.22 CEREBELLAR EFFERENT PATHWAYS

The cerebellum plays an important role in coordinating movement. It influences descending motor pathways to produce fine, smooth, and coordinated motion. The archicerebellum is primarily involved in controlling posture and balance and movement of the head and eyes. It sends efferent fibers to the appropriate descending motor pathways. The paleocerebellum primarily controls movement of the proximal portions of the limbs. It modifies and coordinates these movements through efferent pathways to the appropriate descending motor pathways. The neocerebellum coordinates the movement of the distal portions of the limbs. It helps in the planning of motor activity (e.g., seeing a pencil and then planning and executing the movement of the arm and hand to pick it up).

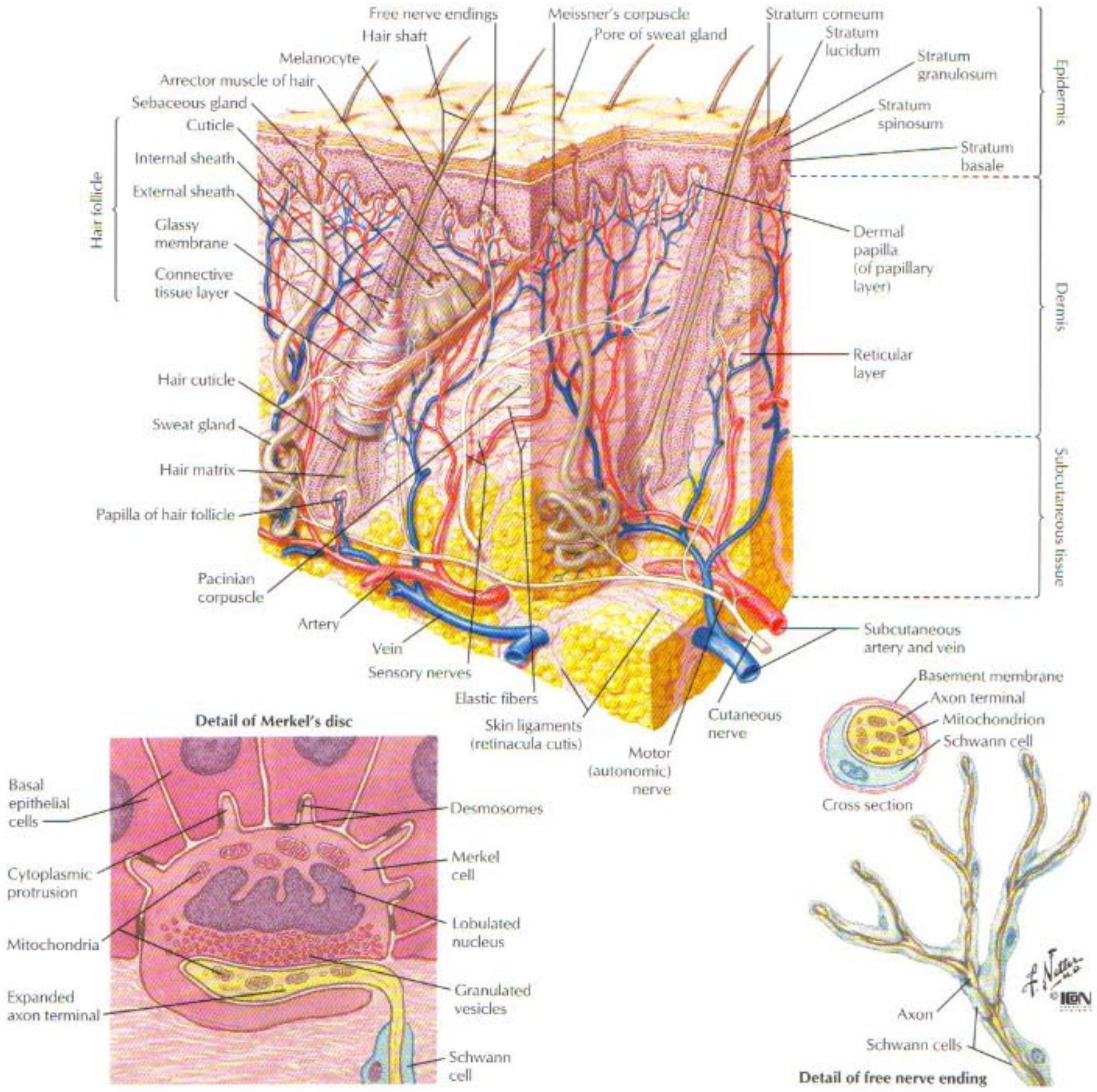
Free nerve endings
Hair shaft
Melanocyte
Arrector muscle of hair
Sebaceous gland
Cuticle
Internal sheath
External sheath
Glassy membrane
Connective tissue layer
Hair follicle
Hair cuticle
Sweat gland
Hair matrix
Papilla of hair follicle
Pacinian corpuscle
Artery
Vein
Sensory nerves
Elastic fibers
Skin ligaments (retinacula cutis)
Motor (autonomic) nerve
Cutaneous nerve
Meissner's corpuscle
Pore of sweat gland
Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Epidermis
Dermal papilla (of papillary layer)
Reticular layer
Dermis
Subcutaneous tissue
Subcutaneous artery and vein
Detail of Merkel's disc
Basal epithelial cells
Cytoplasmic protrusion
Mitochondria
Expanded axon terminal
Desmosomes
Merkel cell
Lobulated nucleus
Granulated vesicles
Schwann cell
Basement membrane
Axon terminal
Mitochondrion
Schwann cell
Cross section
Axon
Schwann cells
Detail of free nerve ending
F. Netter
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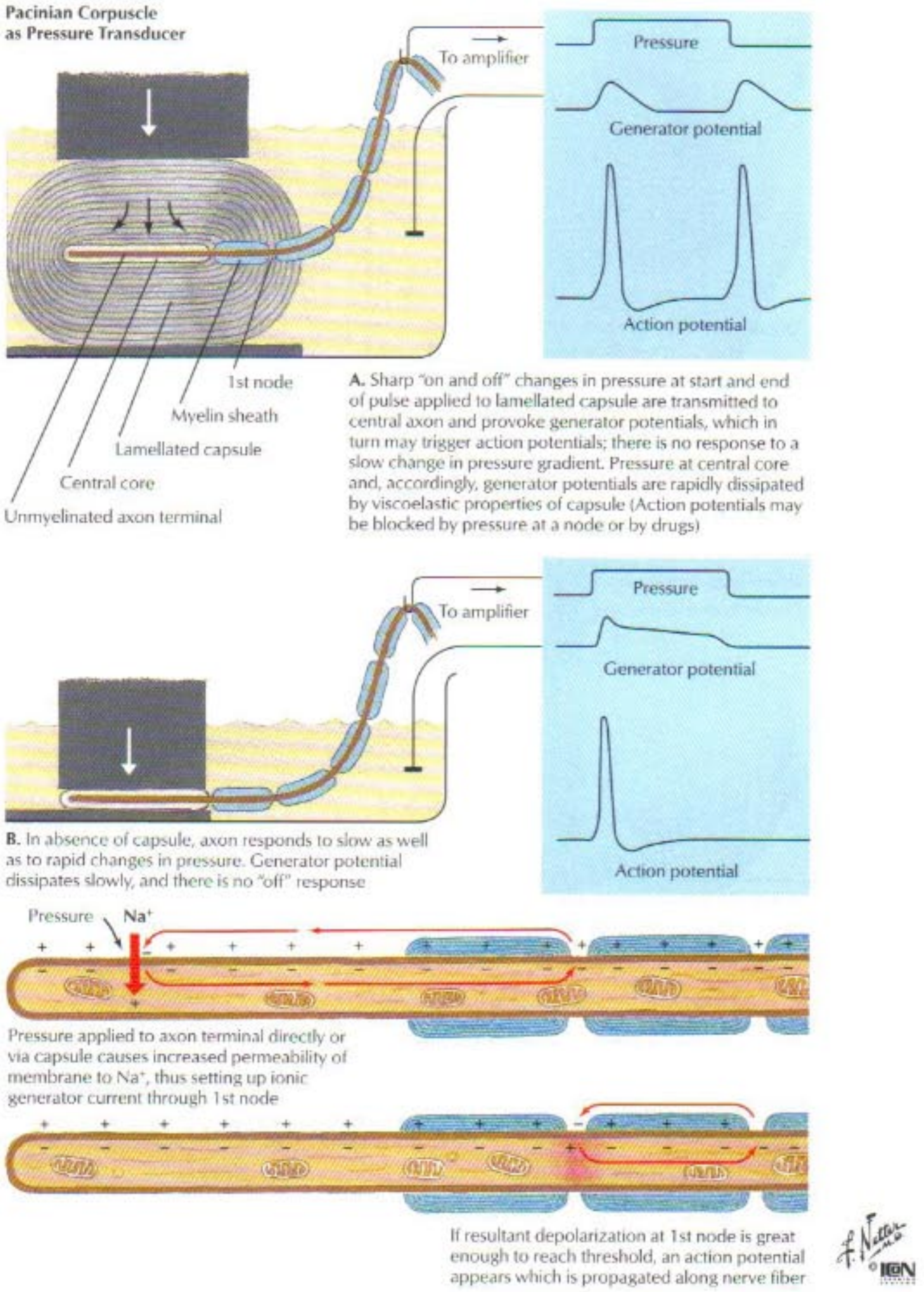
FIGURE 2.23 SKIN AND CUTANEOUS RECEPTORS

Cutaneous receptors respond to touch (mechanoreceptors), pain (nociceptors), and temperature (thermoreceptors). Several different types of receptors are present in skin. Meissner's corpuscles have small receptive fields and respond best to stimuli that are applied at low frequency (i.e., flutter). The pacinian corpuscles are located in the subcutaneous tissue and have large receptive fields. They respond best to high-frequency stimulation (i.e., vibration). Merkel's discs have small receptive fields and respond to touch and pressure (i.e., indenting the skin). Ruffini's corpuscles have large receptive fields, and they also respond to touch and pressure. Free nerve endings respond to pain and temperature.


Pacinian Corpuscle
as Pressure Transducer
To amplifier
Pressure
Generator potential
Action potential
1st node
Myelin sheath
Lamellated capsule
Central core
Unmyelinated axon terminal
To amplifier
Pressure
Generator potential
Action potential
Pressure
Na+

A. Sharp "on and off" changes in pressure at start and end of pulse applied to lamellated capsule are transmitted to central axon and provoke generator potentials, which in turn may trigger action potentials; there is no response to a slow change in pressure gradient. Pressure at central core and, accordingly, generator potentials are rapidly dissipated by viscoelastic properties of capsule (Action potentials may be blocked by pressure at a node or by drugs)

B. In absence of capsule, axon responds to slow as well as to rapid changes in pressure. Generator potential dissipates slowly, and there is no "off" response

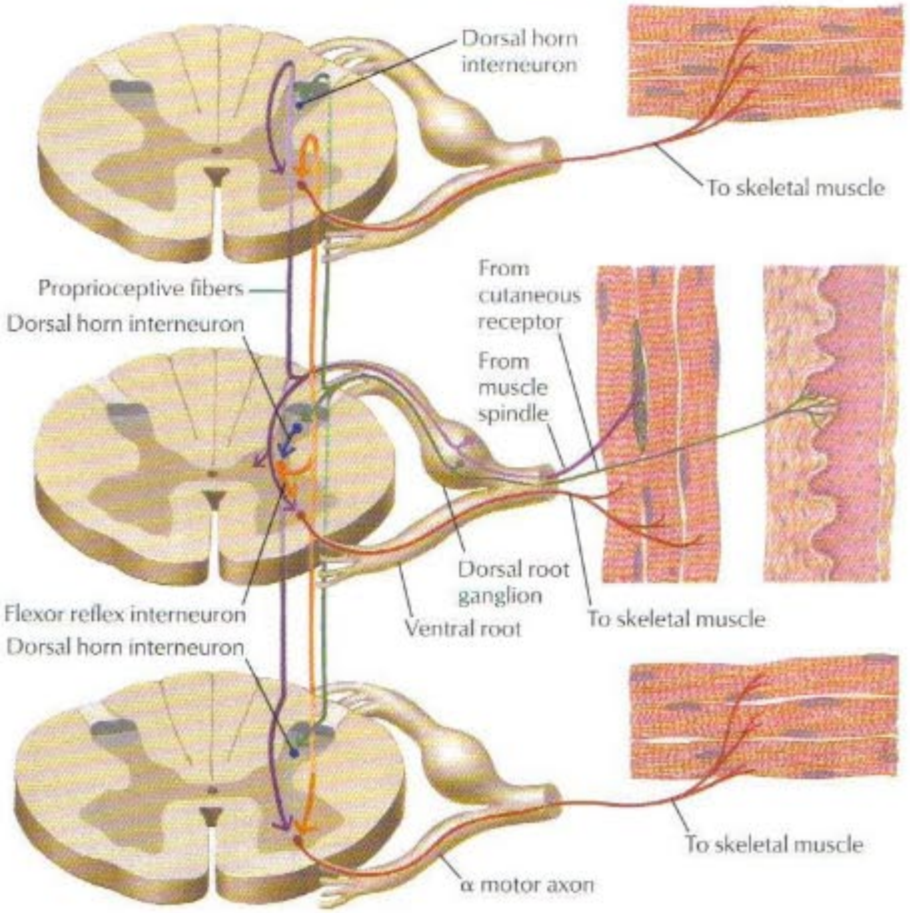
Pressure applied to axon terminal directly or via capsule causes increased permeability of membrane to Na^+, thus setting up ionic generator current through 1st node

If resultant depolarization at 1st node is great enough to reach threshold, an action potential appears which is propagated along nerve fiber

Figure 2.24 Pacinian Corpuscle

Pacinian corpuscles are mechanoreceptors that transduce mechanical forces (displacement, pressure, vibration) into action potentials that are conveyed centrally by afferent nerve fibers. As the viscoelastic lamellae are displaced, the unmyelinated axon terminal membrane's ionic permeability is increased until it is capable of producing a "generator potential." As demonstrated in the figure, pacinian corpuscles respond to the beginning and end of a mechanical force while the concentric lamellae dissipate slow changes in pressure. In the absence of the capsule, the generator potential decays slowly and yields only a single action potential.

Spinal Effector Mechanisms


Dorsal horn interneuron
To skeletal muscle
Proprioceptive fibers
Dorsal horn interneuron
From cutaneous receptor
From muscle spindle
Dorsal root ganglion
Ventral root
To skeletal muscle
Flexor reflex interneuron
Dorsal horn interneuron
To skeletal muscle
α motor axon

Schematic representation of motor neurons

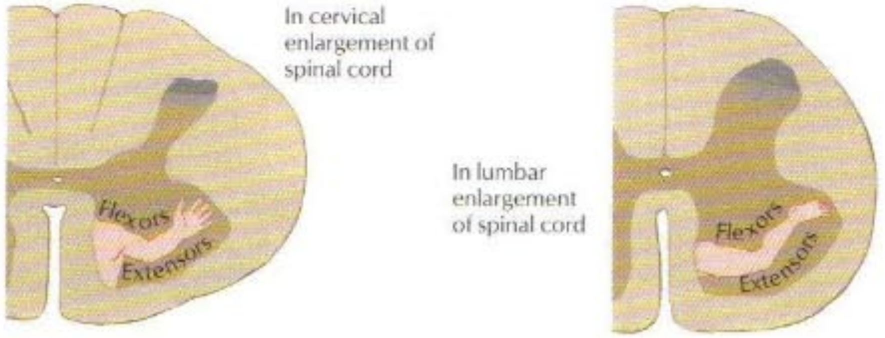

In cervical enlargement of spinal cord
Flexors
Extensors
In lumbar enlargement of spinal cord
Flexors
Extensors
©ICON

FIGURE 2.25 PROPRIOCEPTION: SPINAL EFFECTOR MECHANISM

Position sense or proprioception involves input from cutaneous mechanoreceptors, Golgi tendon organs, and muscle spindles (middle figure of upper panel). Both monosynaptic reflex pathways (middle figure of upper panel) and polysynaptic pathways involving several spinal cord segments (top and bottom figures of upper panel) initiate muscle contraction reflexes. The lower panel shows the somatotopic distribution of the motor neuron cell bodies in the ventral horn of the spinal cord that innervate limb muscles (flexor and extensor muscles of upper and lower limbs).

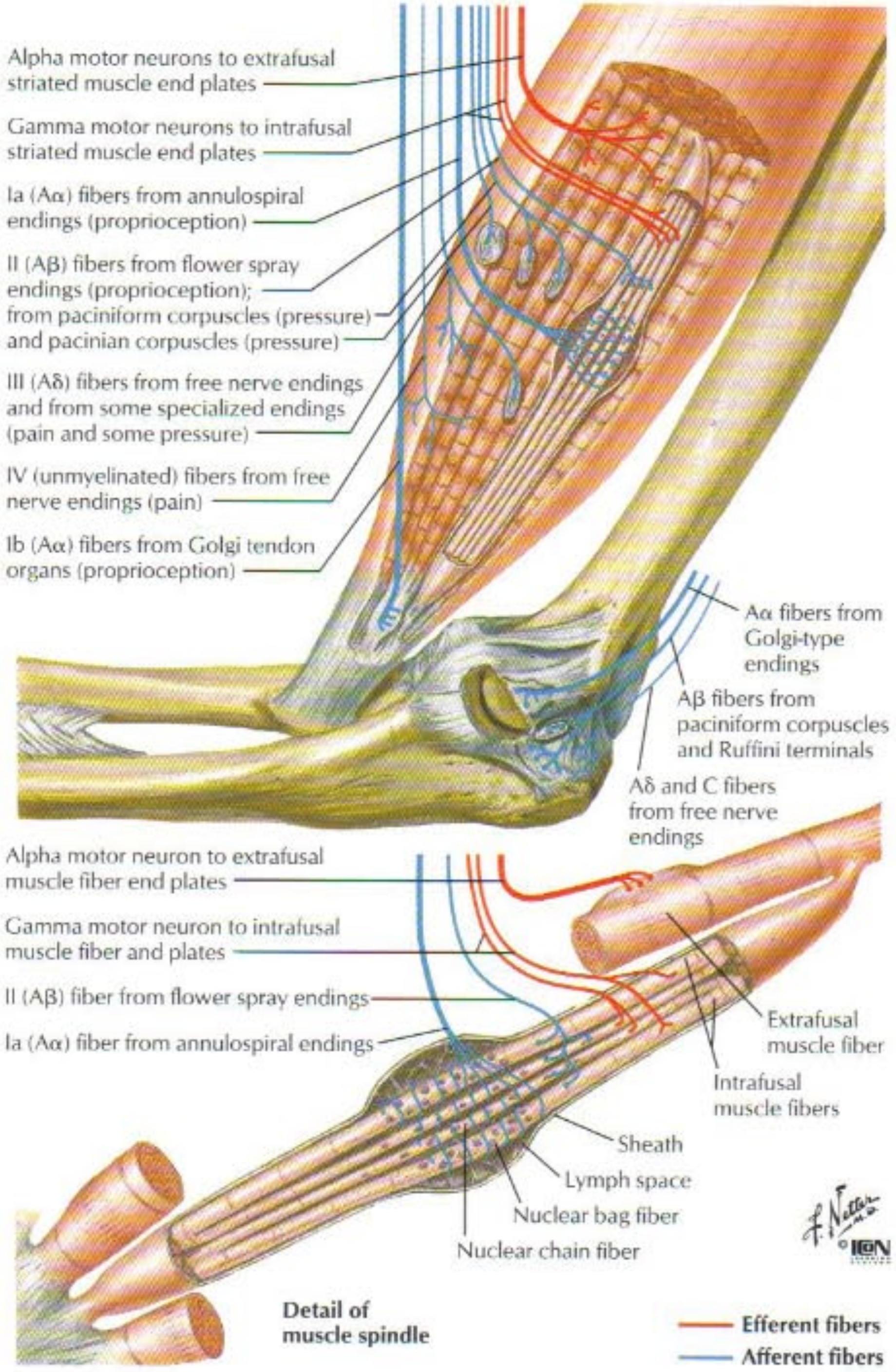

Alpha motor neurons to extrafusal striated muscle end plates
Gamma motor neurons to intrafusal striated muscle end plates
Ia (Aα) fibers from annulospiral endings (proprioception)
II (Aβ) fibers from flower spray endings (proprioception); from paciniform corpuscles (pressure) and pacinian corpuscles (pressure)
III (Aδ) fibers from free nerve endings and from some specialized endings (pain and some pressure)
IV (unmyelinated) fibers from free nerve endings (pain)
Ib (Aα) fibers from Golgi tendon organs (proprioception)
Aα fibers from Golgi-type endings
Aβ fibers from paciniform corpuscles and Ruffini terminals
Aδ and C fibers from free nerve endings
Alpha motor neuron to extrafusal muscle fiber end plates
Gamma motor neuron to intrafusal muscle fiber and plates
II (Aβ) fiber from flower spray endings
Ia (Aα) fiber from annulospiral endings
Extrafusal muscle fiber
Intrafusal muscle fibers
Sheath
Lymph space
Nuclear bag fiber
Nuclear chain fiber
Detail of muscle spindle
Efferent fibers
Afferent fibers
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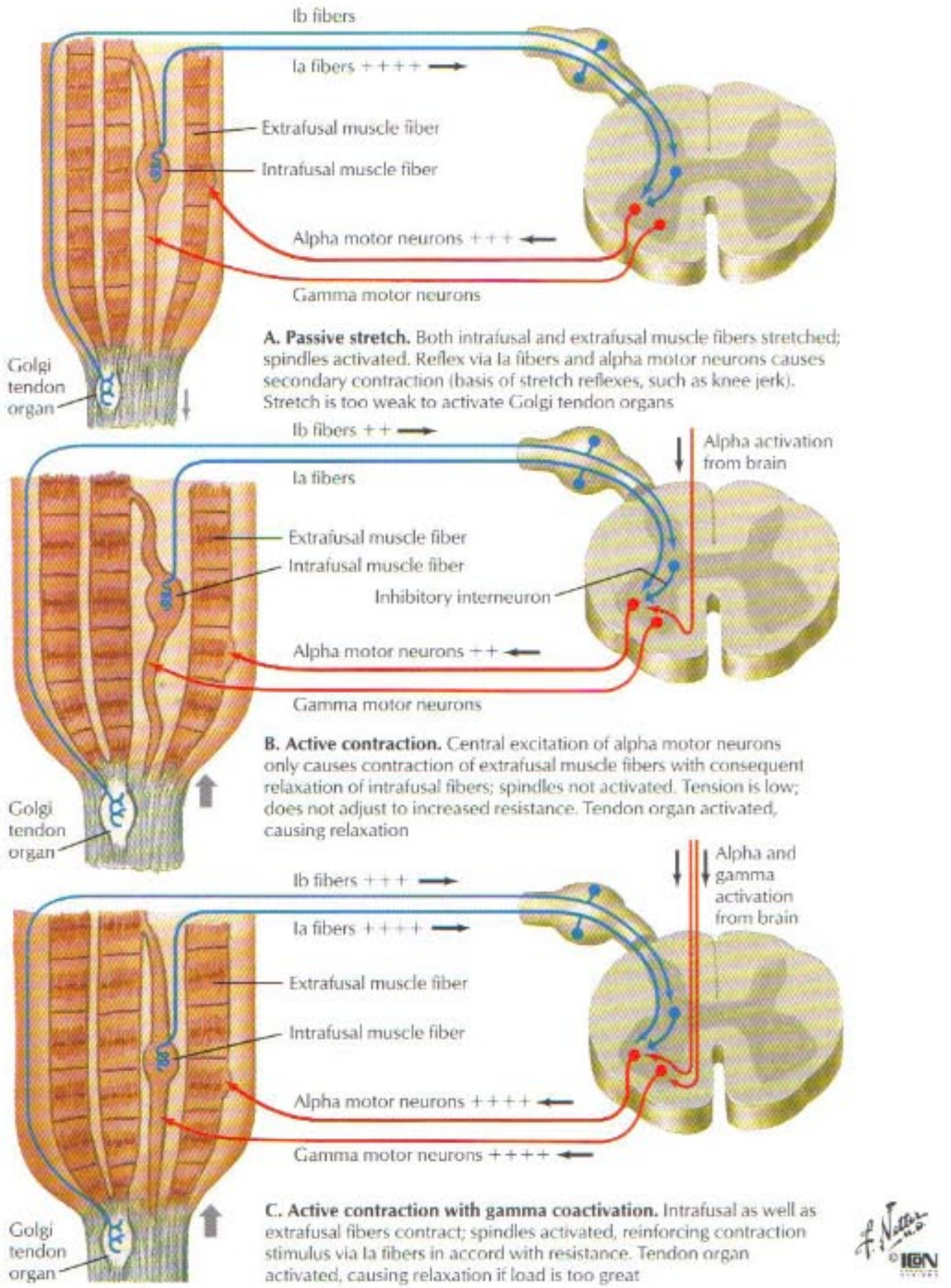
FIGURE 2.26 MUSCLE AND JOINT RECEPTORS

Muscle spindles and Golgi tendon organs send afferent signals to the brain to convey the position of limbs and help coordinate muscle movement. Muscle spindles convey information on muscle tension and contraction (dynamic forces) and muscle length (static forces). The nuclear bag fibers respond to both dynamic and static forces, whereas the nuclear chain fibers respond to static forces. Intrafusal fibers maintain appropriate tension on the nuclear bag and nuclear chain fibers. If the muscle tension is too great (e.g., overstretching of muscle or too heavy a load), activation of the Golgi tendon organ causes a reflex relaxation of the muscle.


Ib fibers
Ia fibers + + + +
Extrafusal muscle fiber
Intrafusal muscle fiber
Alpha motor neurons + + +
Gamma motor neurons
Golgi tendon organ
Ib fibers + +
Ia fibers
Alpha activation from brain
Extrafusal muscle fiber
Intrafusal muscle fiber
Inhibitory interneuron
Alpha motor neurons + +
Gamma motor neurons
Golgi tendon organ
Ib fibers + + +
Ia fibers + + + +
Alpha and gamma activation from brain
Extrafusal muscle fiber
Intrafusal muscle fiber
Alpha motor neurons + + + +
Gamma motor neurons + + + +
Golgi tendon organ
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A. Passive stretch. Both intrafusal and extrafusal muscle fibers stretched; spindles activated. Reflex via Ia fibers and alpha motor neurons causes secondary contraction (basis of stretch reflexes, such as knee jerk). Stretch is too weak to activate Golgi tendon organs

B. Active contraction. Central excitation of alpha motor neurons only causes contraction of extrafusal muscle fibers with consequent relaxation of intrafusal fibers; spindles not activated. Tension is low; does not adjust to increased resistance. Tendon organ activated, causing relaxation

C. Active contraction with gamma coactivation. Intrafusal as well as extrafusal fibers contract; spindles activated, reinforcing contraction stimulus via Ia fibers in accord with resistance. Tendon organ activated, causing relaxation if load is too great

FIGURE 2.27 PROPRIOCEPTIVE REFLEX CONTROL OF MUSCLE TENSION

Interaction of the muscle spindle and Golgi tendon organ during passive stretch of a muscle (panel A) and during a contraction (panels B and C).

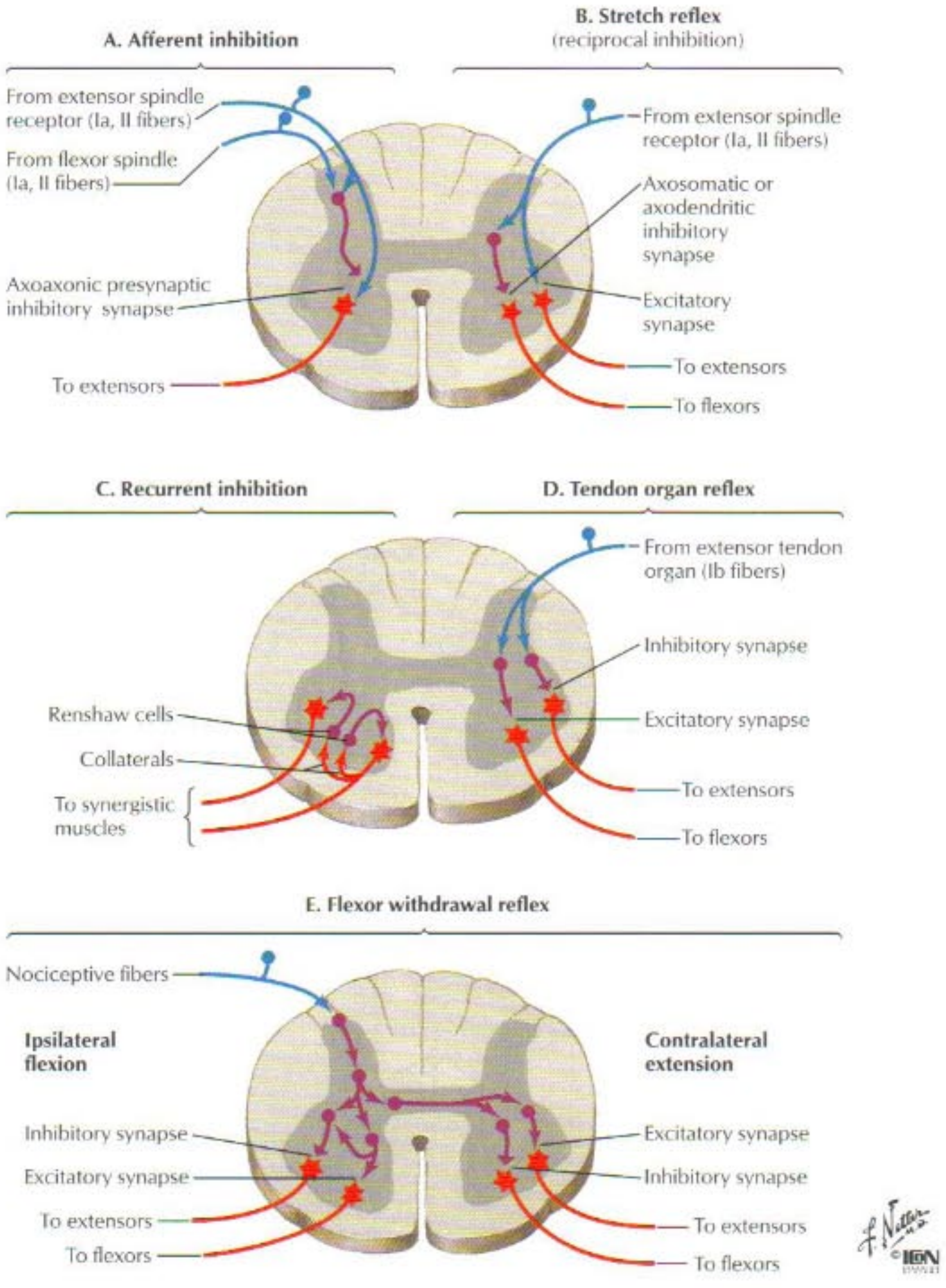
A. Afferent inhibition
From extensor spindle receptor (Ia, II fibers)
From flexor spindle (Ia, II fibers)
Axoaxonic presynaptic inhibitory synapse
To extensors
B. Stretch reflex (reciprocal inhibition)
From extensor spindle receptor (Ia, II fibers)
Axosomatic or axodendritic inhibitory synapse
Excitatory synapse
To extensors
To flexors
C. Recurrent inhibition
Renshaw cells
Collaterals
To synergistic muscles
D. Tendon organ reflex
From extensor tendon organ (Ib fibers)
Inhibitory synapse
Excitatory synapse
To extensors
To flexors
E. Flexor withdrawal reflex
Nociceptive fibers
Ipsilateral flexion
Inhibitory synapse
Excitatory synapse
To extensors
To flexors
Contralateral extension
Excitatory synapse
Inhibitory synapse
To extensors
To flexors
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Figure 2.28 Spinal Reflex Pathways

Summary of the spinal reflex pathways.

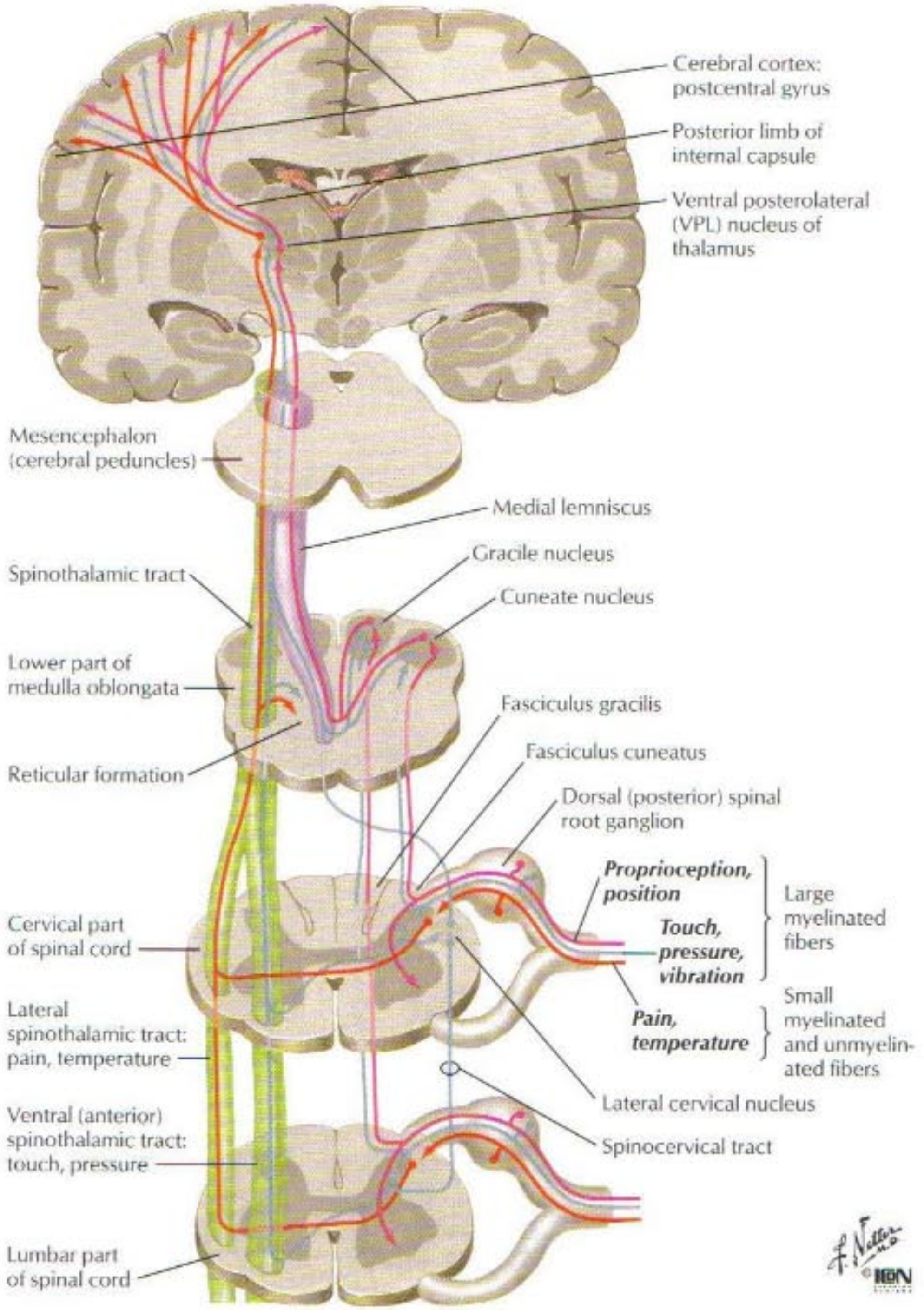

Cerebral cortex: postcentral gyrus
Posterior limb of internal capsule
Ventral posterolateral (VPL) nucleus of thalamus
Mesencephalon (cerebral peduncles)
Medial lemniscus
Gracile nucleus
Cuneate nucleus
Spinothalamic tract
Lower part of medulla oblongata
Fasciculus gracilis
Fasciculus cuneatus
Reticular formation
Dorsal (posterior) spinal root ganglion
Proprioception, position
Touch, pressure, vibration
Large myelinated fibers
Cervical part of spinal cord
Pain, temperature
Small myelinated and unmyelinated fibers
Lateral spinothalamic tract: pain, temperature
Lateral cervical nucleus
Ventral (anterior) spinothalamic tract: touch, pressure
Spinocervical tract
Lumbar part of spinal cord
F. Netter M.D.

FIGURE 2.29 SOMESTHETIC SYSTEM OF THE BODY

Pain, temperature, and pressure sensations below the head ultimately are conveyed to the primary somatosensory cortex (postcentral gyrus) by the anterolateral system (spinothalamic and spinoreticular tracts). The fasciculus gracilis and cuneatus of the spinal lemniscal system convey proprioceptive, vibratory, and tactile sensations to the thalamus (ventral posterolateral nucleus), whereas the lateral cervical system mediates some touch, vibratory, and proprioceptive sensations (blue and purple lines show these dual pathways). Ultimately, these fibers ascend as parallel pathways to the thalamus, synapse, and ascend to the cortex.

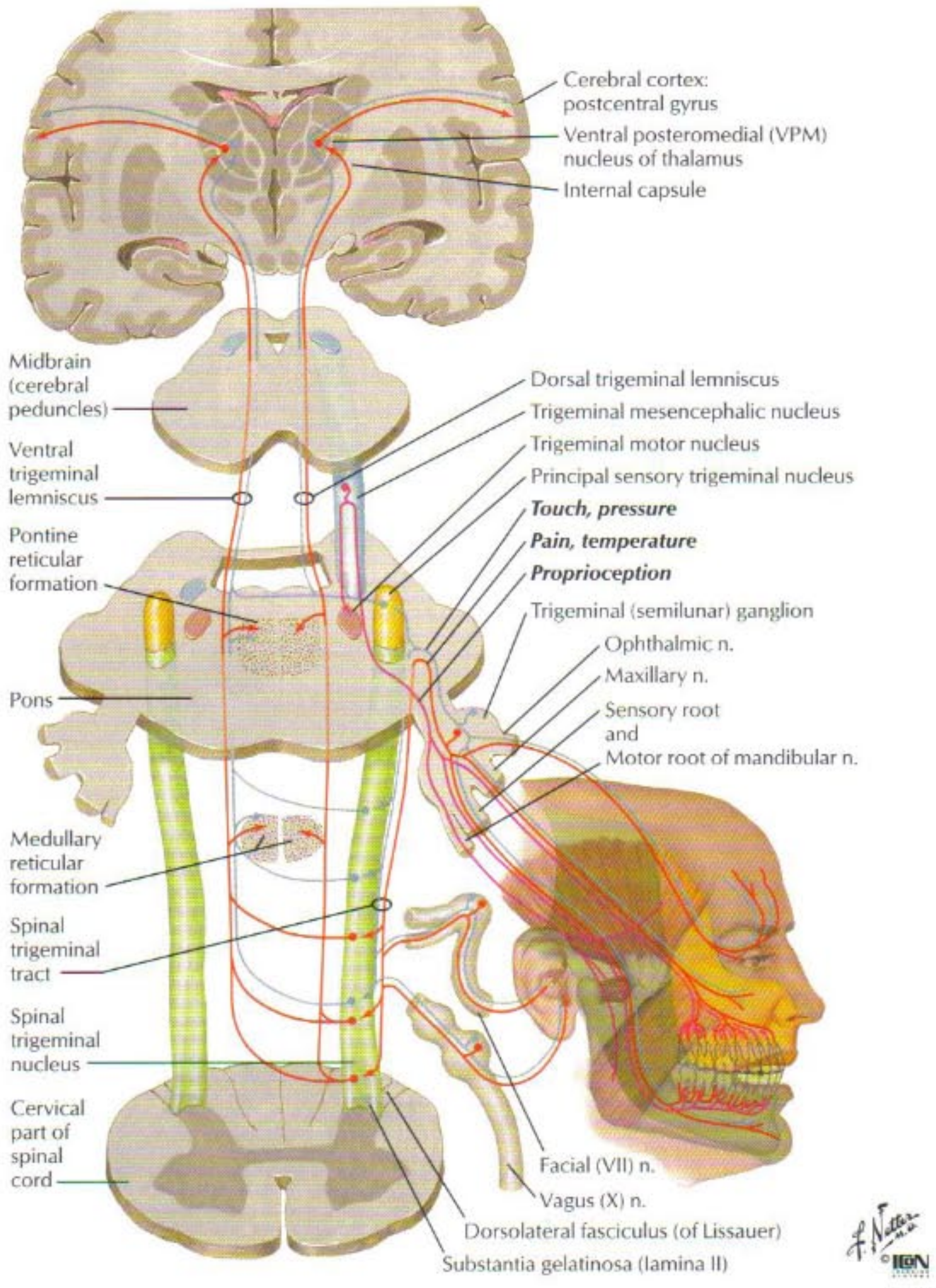
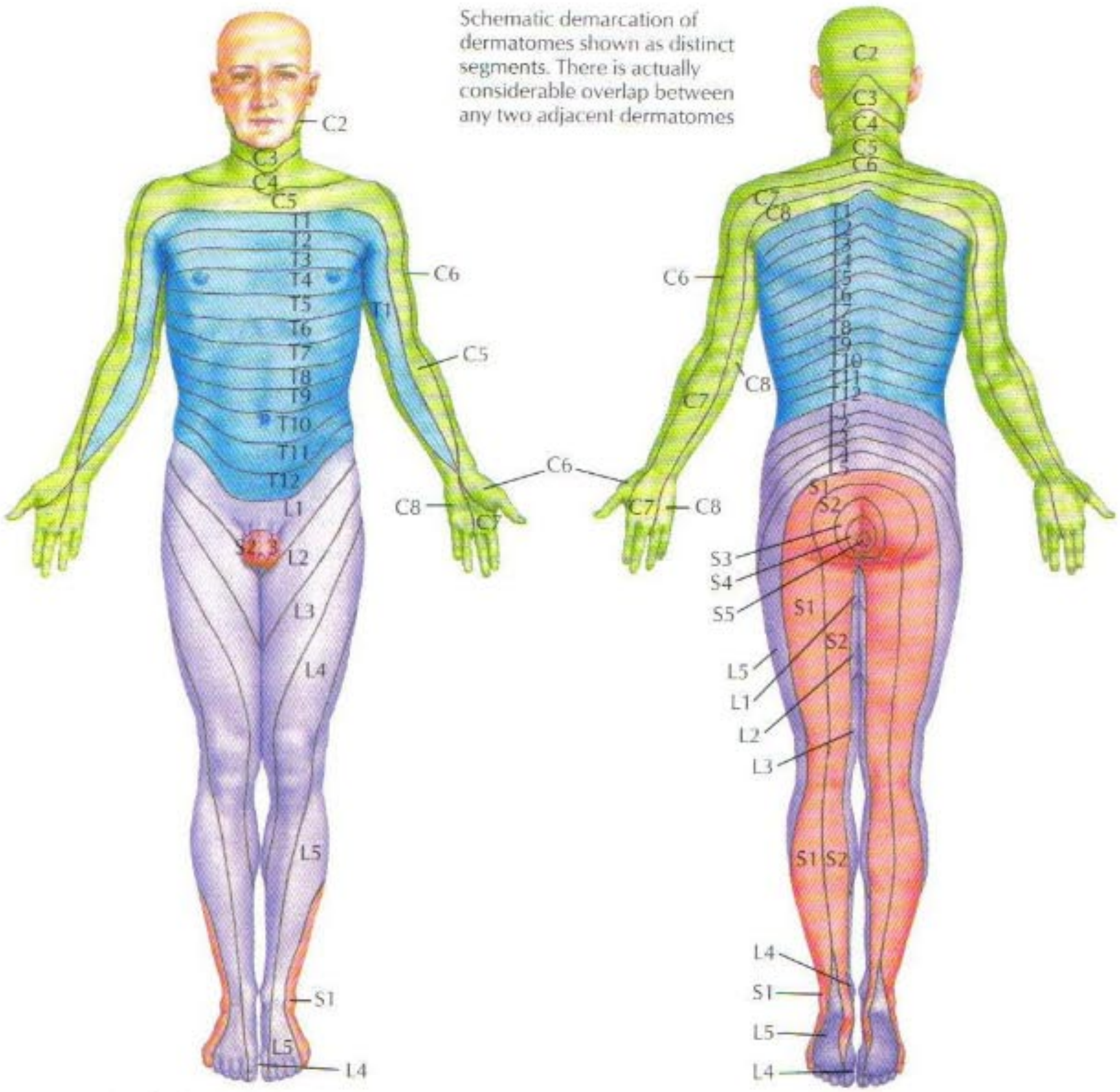

Cerebral cortex: postcentral gyrus
Ventral posteromedial (VPM) nucleus of thalamus
Internal capsule
Midbrain (cerebral peduncles)
Ventral trigeminal lemniscus
Pontine reticular formation
Pons
Medullary reticular formation
Spinal trigeminal tract
Spinal trigeminal nucleus
Cervical part of spinal cord
Dorsal trigeminal lemniscus
Trigeminal mesencephalic nucleus
Trigeminal motor nucleus
Principal sensory trigeminal nucleus
Touch, pressure
Pain, temperature
Proprioception
Trigeminal (semilunar) ganglion
Ophthalmic n.
Maxillary n.
Sensory root and Motor root of mandibular n.
Facial (VII) n.
Vagus (X) n.
Dorsolateral fasciculus (of Lissauer)
Substantia gelatinosa (lamina II)

FIGURE 2.30 SOMESTHETIC SYSTEM OF THE HEAD

Nerve cells bodies for touch, pressure, pain, and temperature in the head are in the trigeminal (semilunar) ganglion of the trigeminal (CN V) nerve (blue and red lines in figure). Neuronal cell bodies mediating proprioception reside in the mesencephalic nucleus of CN V (purple fibers). Most relay neurons project to the contralateral VPM nucleus of the thalamus and thence to the postcentral gyrus of the cerebral cortex, where they are somatotopically represented.



Schematic demarcation of dermatomes shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes

C2
C3
C4
C5
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
S2, 3
L2
L3
L4
L5
S1
L5
L4
C6
T1
C5
C6
C8
C7
C2
C3
C4
C5
C6
C7
C8
C6
C8
C7
C6
C7
C8
S1
S2
S3
S4
S5
S1
S2
L5
L1
L2
L3
S1
S2
L4
S1
L5
L4

Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5, S1	Foot
L4	Medial side of great toe
S1, 2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

FIGURE 2.31 DERMATOMES

Sensory information below the head is localized to specific areas of the body, which reflect the distribution of peripheral sensory fibers that convey sensations to the spinal cord through the dorsal roots (sensory nerve cell bodies reside in the corresponding dorsal root ganglion). The area of skin subserved by afferent fibers of one dorsal root is called a dermatome. This figure shows the dermatome segments and lists key dermatome levels used by clinicians. Variability and overlap occur, so all dermatome segments are only approximations.

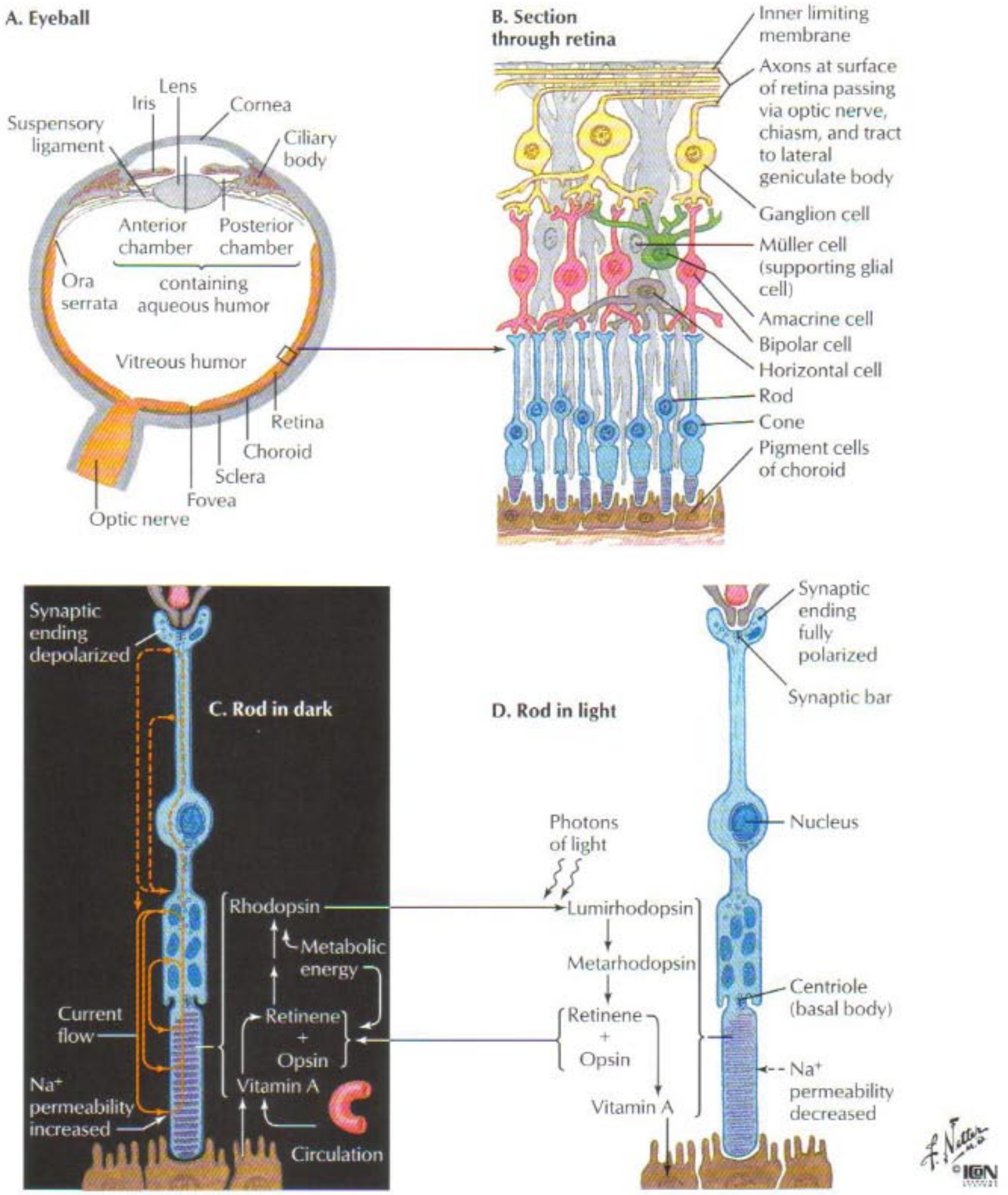

A. Eyeball
Lens
Iris
Cornea
Suspensory ligament
Ciliary body
Anterior chamber
Posterior chamber
containing aqueous humor
Ora serrata
Vitreous humor
Retina
Choroid
Sclera
Fovea
Optic nerve
B. Section through retina
Inner limiting membrane
Axons at surface of retina passing via optic nerve, chiasm, and tract to lateral geniculate body
Ganglion cell
Müller cell (supporting glial cell)
Amacrine cell
Bipolar cell
Horizontal cell
Rod
Cone
Pigment cells of choroid
Synaptic ending depolarized
C. Rod in dark
Current flow
Na+ permeability increased
Rhodopsin
Metabolic energy
Retinene + Opsin
Vitamin A
Circulation
D. Rod in light
Photons of light
Lumirhodopsin
Metarhodopsin
Retinene + Opsin
Vitamin A
Synaptic ending fully polarized
Synaptic bar
Nucleus
Centriole (basal body)
Na+ permeability decreased

FIGURE 2.32 VISUAL RECEPTORS

The rods and cones of the retina transduce light into electrical signals. As illustrated for the rod, light is absorbed by rhodopsin, and through the second messenger cGMP (not shown), Na^+ channels in the membrane close and the cell hyperpolarizes. Thus, in the dark the cell is depolarized, but it is hyperpolarized in the light. This electrical response to light is distinct from other receptor responses, in which the response to a stimulus results in a depolarization of the receptor cell membrane.

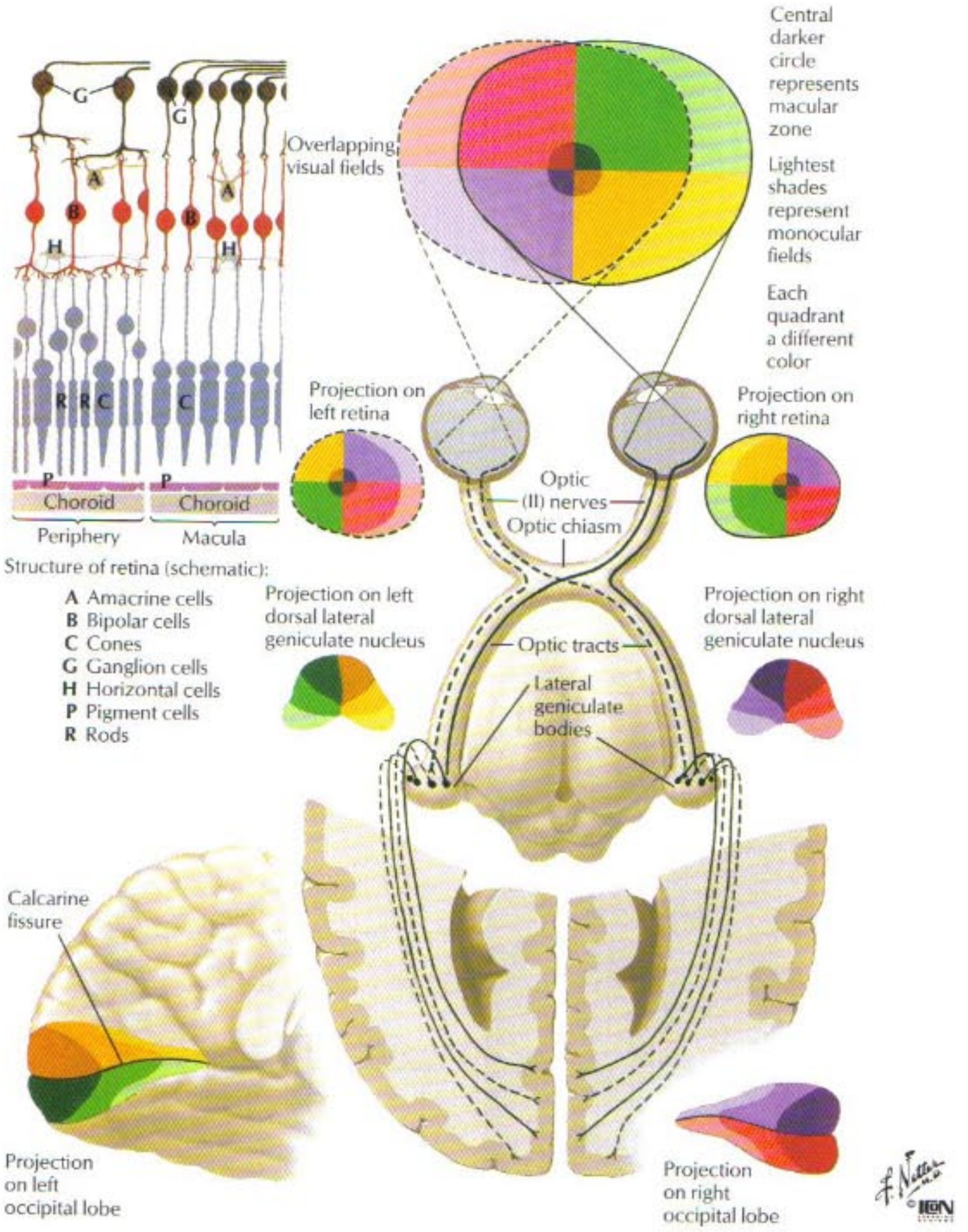

Central darker circle represents macular zone
Lightest shades represent monocular fields
Each quadrant a different color
Overlapping visual fields
G
A
B
H
R
C
P
Choroid
Periphery
Macula
Structure of retina (schematic):
A Amacrine cells
B Bipolar cells
C Cones
G Ganglion cells
H Horizontal cells
P Pigment cells
R Rods
Projection on left retina
Projection on right retina
Optic (II) nerves
Optic chiasm
Projection on left dorsal lateral geniculate nucleus
Projection on right dorsal lateral geniculate nucleus
Optic tracts
Lateral geniculate bodies
Calcarine fissure
Projection on left occipital lobe
Projection on right occipital lobe
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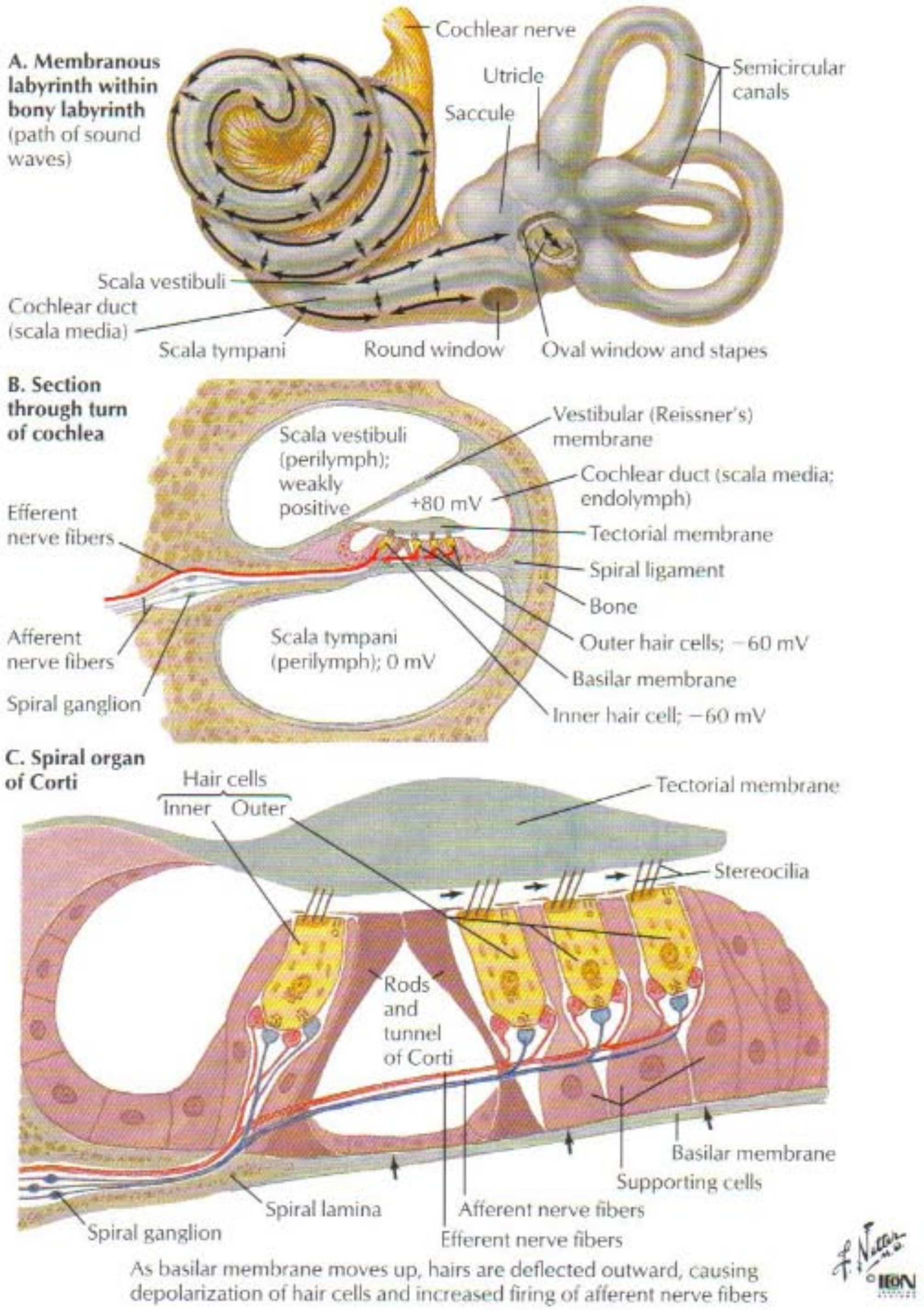
FIGURE 2.33 RETINOGENICULOSTRIATE VISUAL PATHWAY

The retina has two types of photoreceptors: cones that mediate color vision and rods that mediate light perception but with low acuity. The greatest acuity is found in the region of the macula of the retina, where only cones are found (upper left panel). Visual signals are conveyed by the ganglion cells whose axons course in the optic nerves. Visual signals from the nasal retina cross in the optic chiasm while information from the temporal retina remains in the ipsilateral optic tract. Fibers synapse in the lateral geniculate nucleus (visual field is topographically represented here and inverted), and signals are conveyed to the visual cortex on the medial surface of the occipital lobe.


A. Membranous labyrinth within bony labyrinth
(path of sound waves)
Cochlear nerve
Utricle
Saccule
Semicircular canals
Scala vestibuli
Cochlear duct (scala media)
Scala tympani
Round window
Oval window and stapes
B. Section through turn of cochlea
Scala vestibuli (perilymph); weakly positive
+80 mV
Vestibular (Reissner's) membrane
Cochlear duct (scala media; endolymph)
Tectorial membrane
Spiral ligament
Bone
Outer hair cells; −60 mV
Basilar membrane
Inner hair cell; −60 mV
Efferent nerve fibers
Afferent nerve fibers
Spiral ganglion
Scala tympani (perilymph); 0 mV
C. Spiral organ of Corti
Hair cells
Inner
Outer
Tectorial membrane
Stereocilia
Rods and tunnel of Corti
Basilar membrane
Supporting cells
Afferent nerve fibers
Efferent nerve fibers
Spiral lamina
Spiral ganglion
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As basilar membrane moves up, hairs are deflected outward, causing depolarization of hair cells and increased firing of afferent nerve fibers

FIGURE 2.34 COCHLEAR RECEPTORS

The cochlea transduces sound into electrical signals. This is accomplished by the hair cells, which depolarize in response to vibration of the basilar membrane. The basilar membrane moves in response to pressure changes imparted on the oval window of the cochlea in response to vibrations of the tympanic membrane.

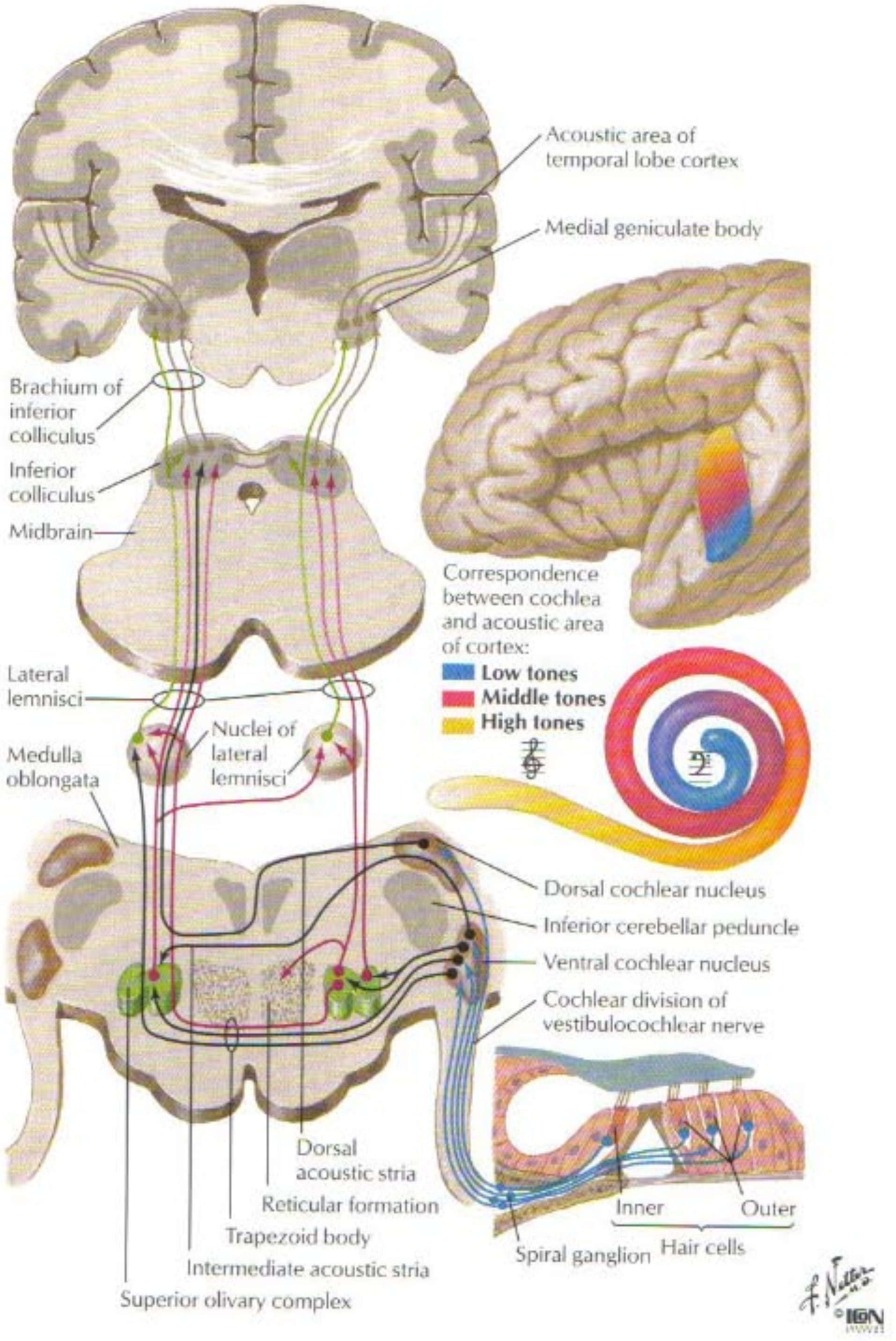
Acoustic area of temporal lobe cortex
Medial geniculate body
Brachium of inferior colliculus
Inferior colliculus
Midbrain
Correspondence between cochlea and acoustic area of cortex:
🟦 Low tones
🟥 Middle tones
🟨 High tones
Lateral lemnisci
Nuclei of lateral lemnisci
Medulla oblongata
Dorsal cochlear nucleus
Inferior cerebellar peduncle
Ventral cochlear nucleus
Cochlear division of vestibulocochlear nerve
Dorsal acoustic stria
Reticular formation
Trapezoid body
Intermediate acoustic stria
Superior olivary complex
Inner
Outer
Hair cells
Spiral ganglion

FIGURE 2.35 AUDITORY PATHWAYS

The cochlea transduces sound into electrical signals. Axons convey these signals to the dorsal and ventral cochlear nuclei, where it is tonotopically organized. Following a series of integrated relay pathways, the ascending pathway projects to the thalamus (medial geniculate bodies) and then the acoustic cortex in the transverse gyrus of the temporal lobe, where information is tonotopically represented (low, middle, and high tones).

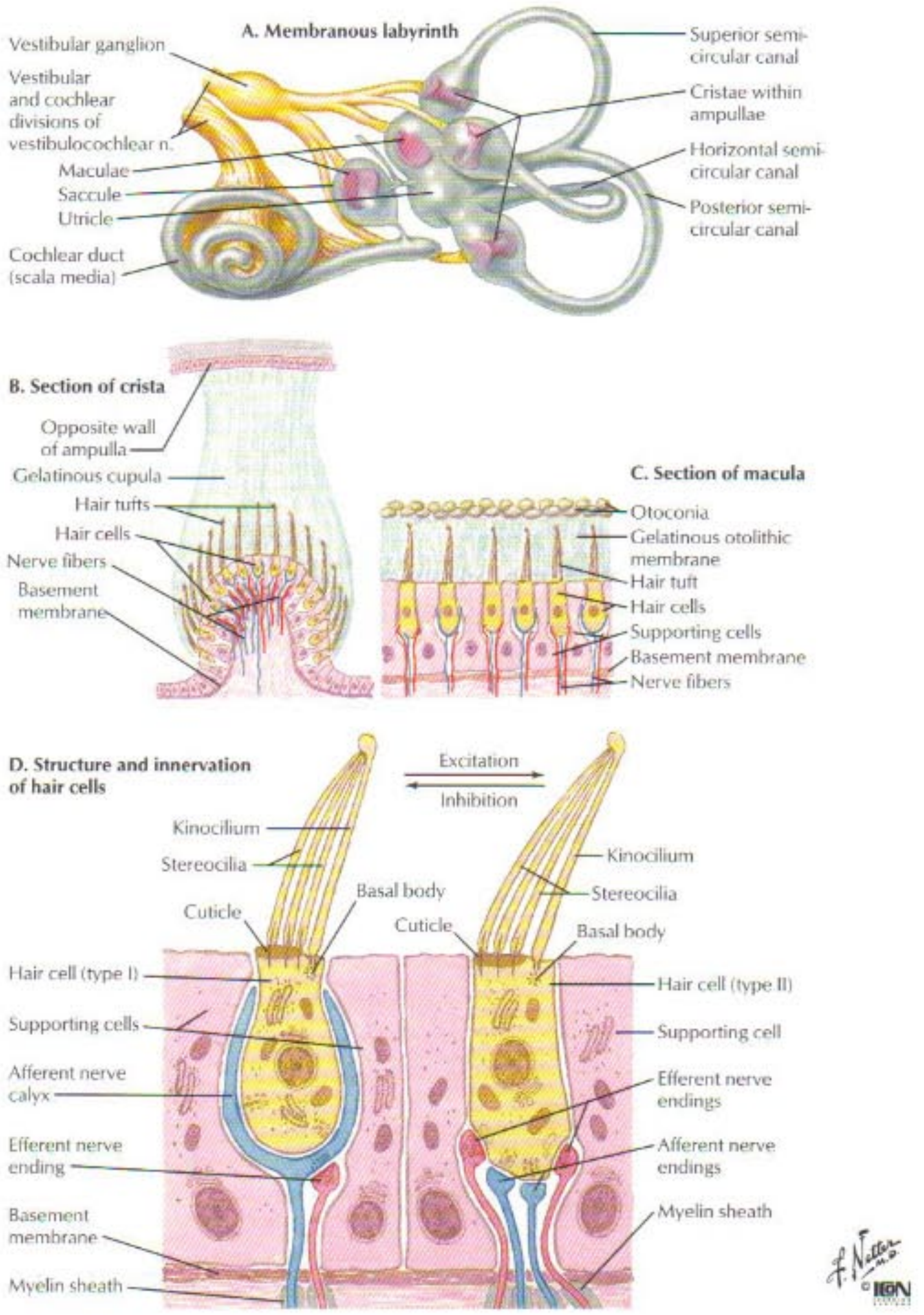
A. Membranous labyrinth
Vestibular ganglion
Vestibular and cochlear divisions of vestibulocochlear n.
Maculae
Saccule
Utricle
Cochlear duct (scala media)
Superior semicircular canal
Cristae within ampullae
Horizontal semicircular canal
Posterior semicircular canal
B. Section of crista
Opposite wall of ampulla
Gelatinous cupula
Hair tufts
Hair cells
Nerve fibers
Basement membrane
C. Section of macula
Otoconia
Gelatinous otolithic membrane
Hair tuft
Hair cells
Supporting cells
Basement membrane
Nerve fibers
D. Structure and innervation of hair cells
Excitation
Inhibition
Kinocilium
Stereocilia
Cuticle
Basal body
Cuticle
Kinocilium
Stereocilia
Basal body
Hair cell (type I)
Supporting cells
Afferent nerve calyx
Efferent nerve ending
Basement membrane
Myelin sheath
Hair cell (type II)
Supporting cell
Efferent nerve endings
Afferent nerve endings
Myelin sheath

FIGURE 2.36 VESTIBULAR RECEPTORS

The vestibular apparatus detects movement of the head in the form of linear and angular acceleration. This information is important for the control of eye movements so that the retina can be provided with a stable visual image. It is also important for the control of posture. The utricle and saccule respond to linear acceleration, such as the pull of gravity. The three semicircular canals are aligned so that the angular movement of the head can be sensed in all planes. The sensory hair cells are located in the maculae of the utricle and saccule (panel A; higher power view of the macula is shown in panel C), and in the cristae within each ampullae of the semicircular canals (panel A; higher power view of the crista is shown in panel B).

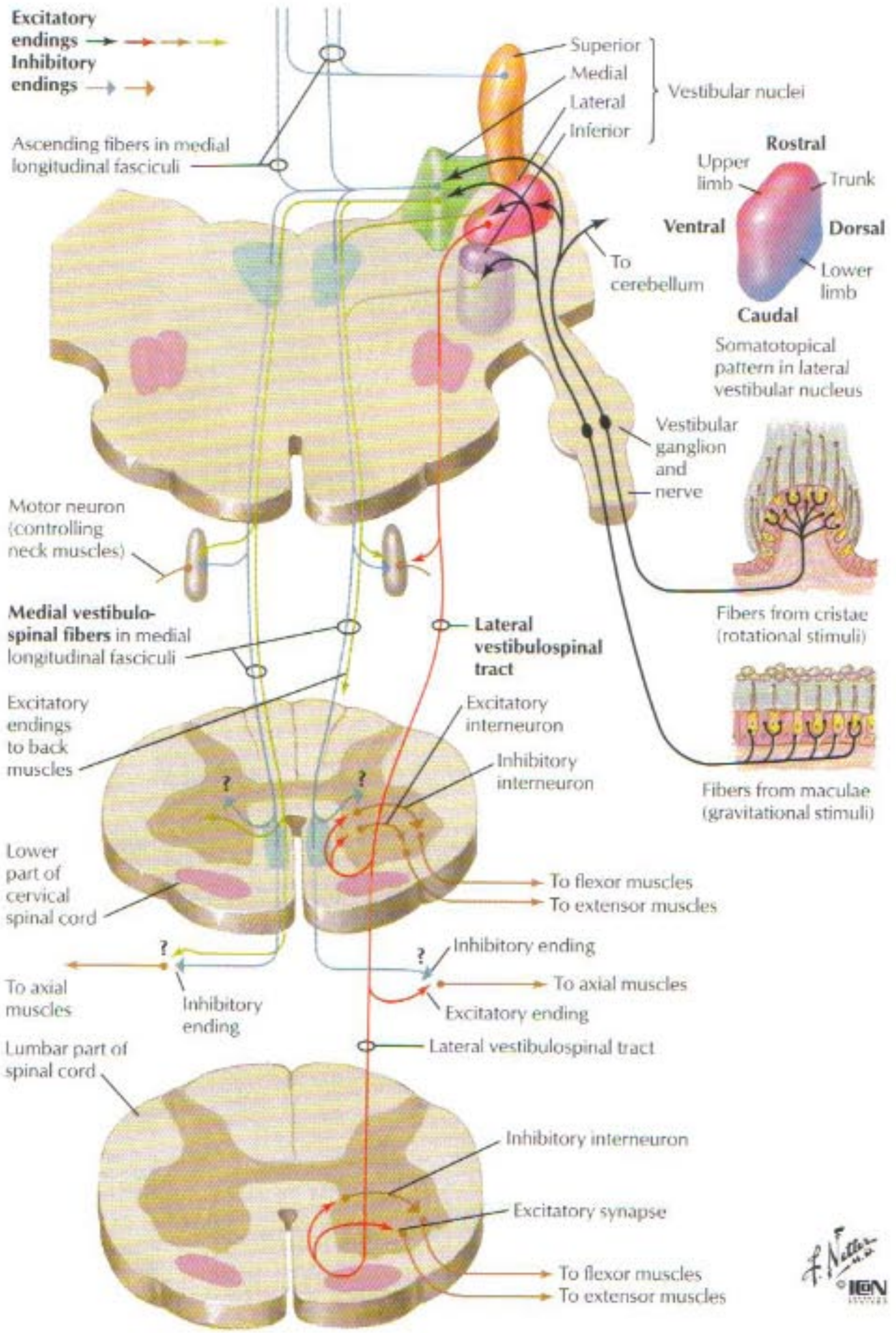
Excitatory endings
Inhibitory endings
Ascending fibers in medial longitudinal fasciculi
Superior
Medial
Lateral
Inferior
Vestibular nuclei
Rostral
Upper limb
Trunk
Ventral
Dorsal
Lower limb
Caudal
Somatotopical pattern in lateral vestibular nucleus
To cerebellum
Vestibular ganglion and nerve
Motor neuron (controlling neck muscles)
Medial vestibulospinal fibers in medial longitudinal fasciculi
Lateral vestibulospinal tract
Fibers from cristae (rotational stimuli)
Excitatory endings to back muscles
Excitatory interneuron
Inhibitory interneuron
Fibers from maculae (gravitational stimuli)
Lower part of cervical spinal cord
To flexor muscles
To extensor muscles
?
Inhibitory ending
To axial muscles
Inhibitory ending
To axial muscles
Excitatory ending
Lumbar part of spinal cord
Lateral vestibulospinal tract
Inhibitory interneuron
Excitatory synapse
To flexor muscles
To extensor muscles
F. Netter M.D.
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FIGURE 2.37 VESTIBULOSPINAL TRACTS

Sensory input from the vestibular apparatus is used to maintain stability of the head and to maintain balance and posture. Axons convey vestibular information to the vestibular nuclei in the pons, and then secondary axons distribute this information to five sites: spinal cord (muscle control), cerebellum (vermis), reticular formation (vomiting center), extraocular muscles, and cortex (conscious perception). This figure shows only the spinal cord pathways.

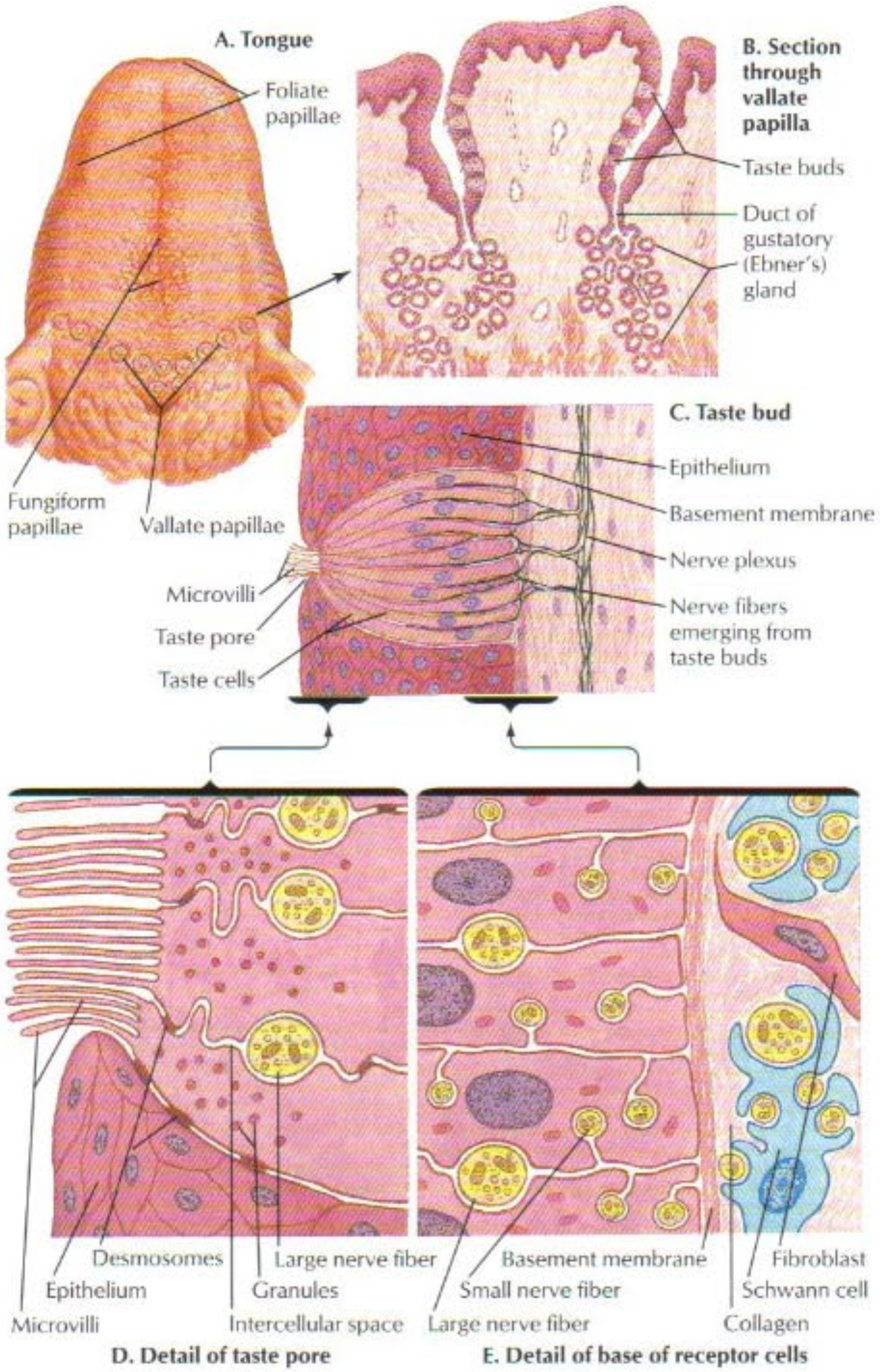
A. Tongue
Foliate papillae
Fungiform papillae
Vallate papillae
B. Section through vallate papilla
Taste buds
Duct of gustatory (Ebner's) gland
C. Taste bud
Epithelium
Basement membrane
Nerve plexus
Nerve fibers emerging from taste buds
Microvilli
Taste pore
Taste cells
Desmosomes
Epithelium
Microvilli
Large nerve fiber
Granules
Intercellular space
Basement membrane
Small nerve fiber
Large nerve fiber
Fibroblast
Schwann cell
Collagen
D. Detail of taste pore
E. Detail of base of receptor cells

FIGURE 2.38 TASTE RECEPTORS

Taste buds on the tongue respond to various chemical stimuli. Taste cells, like neurons, normally have a net negative charge internally and are depolarized by stimuli, thus releasing transmitters that depolarize neurons connected to the taste cells. A single taste bud can respond to more than one stimulus. The four traditional taste qualities that are sensed are sweet, salty, sour, and bitter.

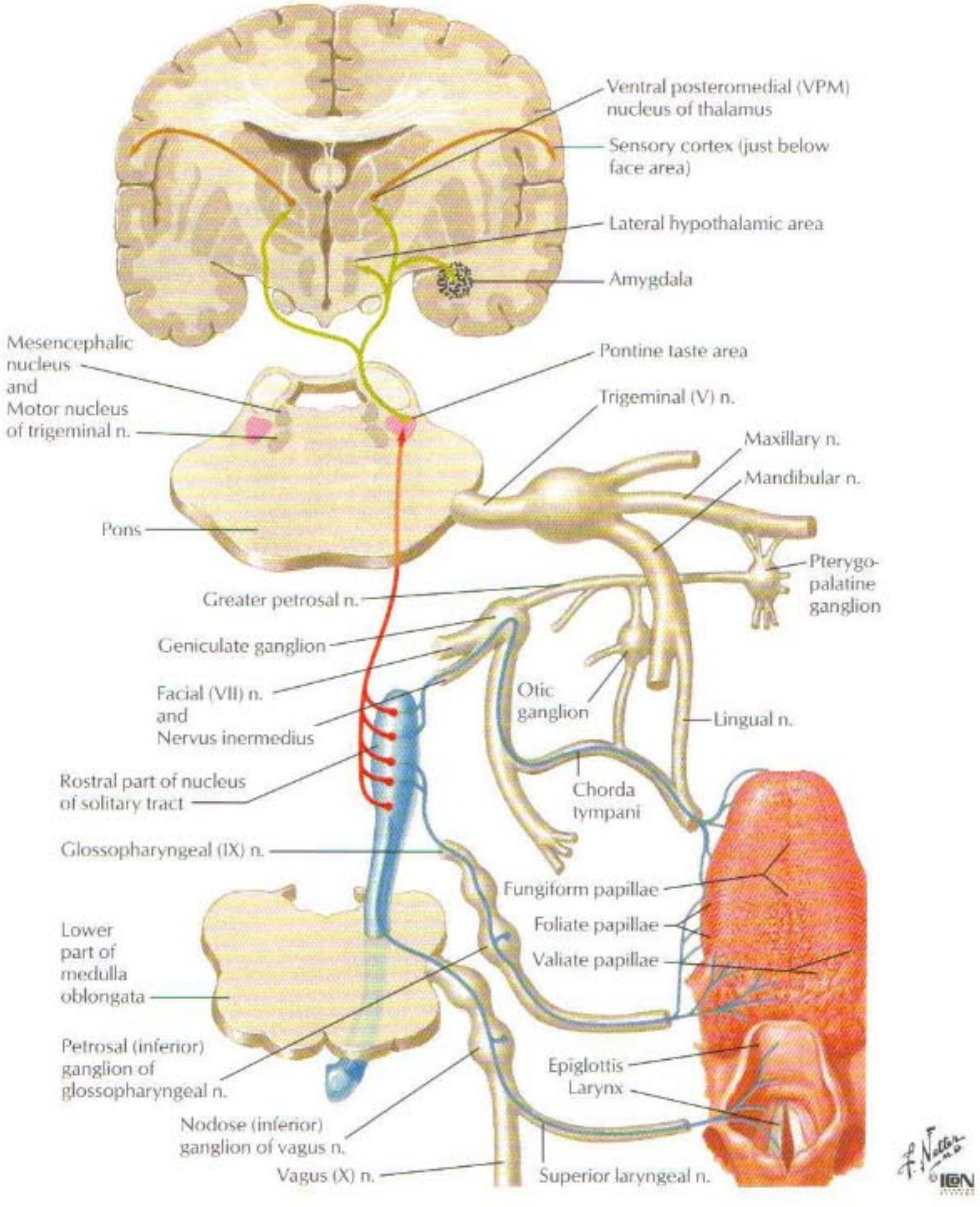
Ventral posteromedial (VPM) nucleus of thalamus
Sensory cortex (just below face area)
Lateral hypothalamic area
Amygdala
Mesencephalic nucleus and Motor nucleus of trigeminal n.
Pontine taste area
Trigeminal (V) n.
Maxillary n.
Mandibular n.
Pons
Pterygo-palatine ganglion
Greater petrosal n.
Geniculate ganglion
Facial (VII) n. and Nervus inermedius
Otic ganglion
Lingual n.
Rostral part of nucleus of solitary tract
Chorda tympani
Glossopharyngeal (IX) n.
Fungiform papillae
Foliate papillae
Valiate papillae
Lower part of medulla oblongata
Petrosal (inferior) ganglion of glossopharyngeal n.
Epiglottis
Larynx
Nodose (inferior) ganglion of vagus n.
Vagus (X) n.
Superior laryngeal n.

FIGURE 2.39 TASTE PATHWAYS

Depicted here are the afferent pathways leading from the taste receptors to the brainstem and, ultimately, to the sensory cortex in the post-central gyrus.

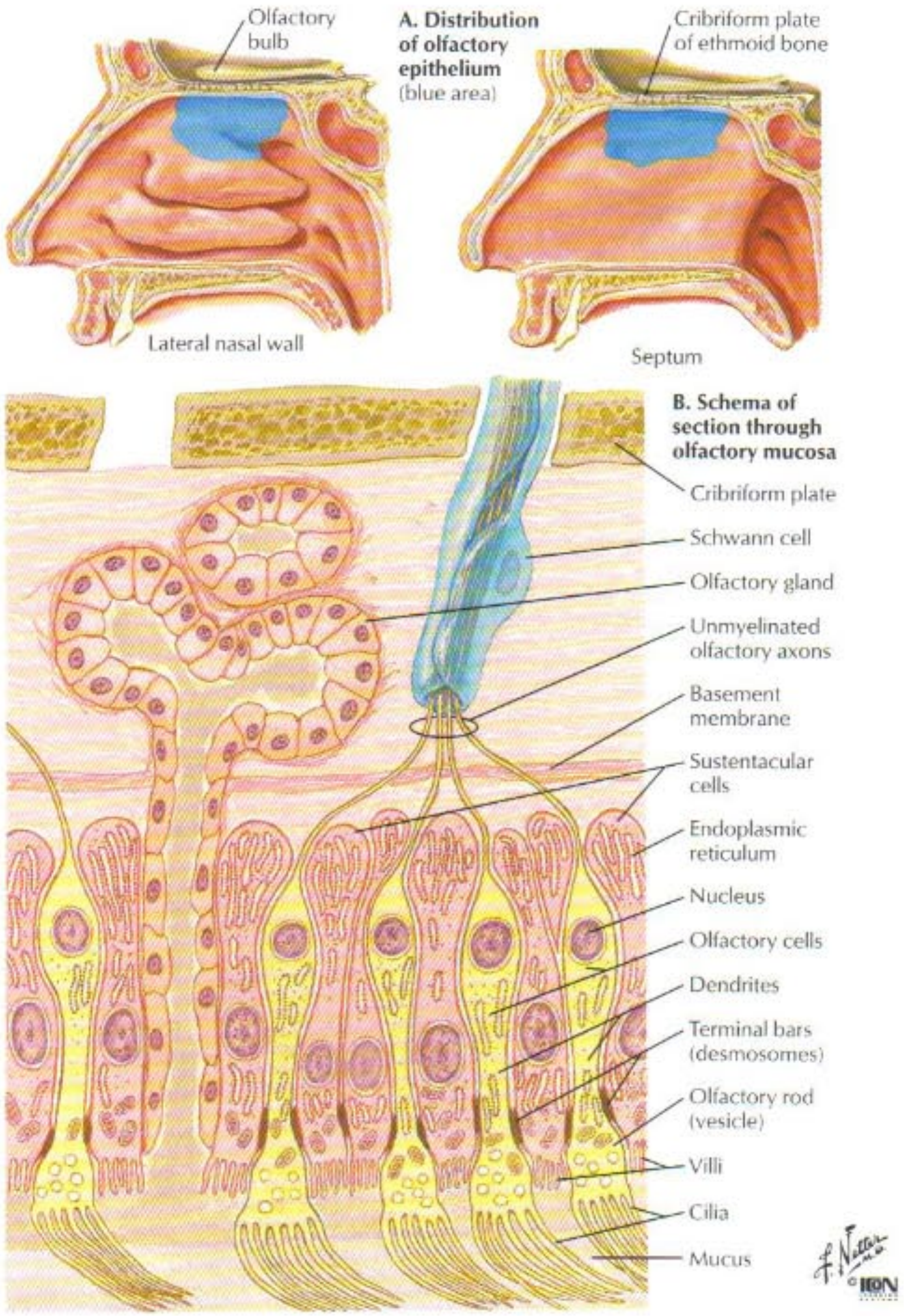
Olfactory bulb
A. Distribution of olfactory epithelium (blue area)
Cribriform plate of ethmoid bone
Lateral nasal wall
Septum
B. Schema of section through olfactory mucosa
Cribriform plate
Schwann cell
Olfactory gland
Unmyelinated olfactory axons
Basement membrane
Sustentacular cells
Endoplasmic reticulum
Nucleus
Olfactory cells
Dendrites
Terminal bars (desmosomes)
Olfactory rod (vesicle)
Villi
Cilia
Mucus

FIGURE 2.40 OLFACTORY RECEPTORS

The sensory cells that make up the olfactory epithelium respond to odorants by depolarizing. Like taste buds, an olfactory cell can respond to more than one odorant. There are six general odor qualities that can be sensed: floral, ethereal (e.g., pears), musky, camphor (e.g., eucalyptus), putrid, and pungent (e.g., vinegar, peppermint). Secretions from the olfactory glands (Bowman's glands) trap odorants as well as remove old odorants so that new scents may be detected.

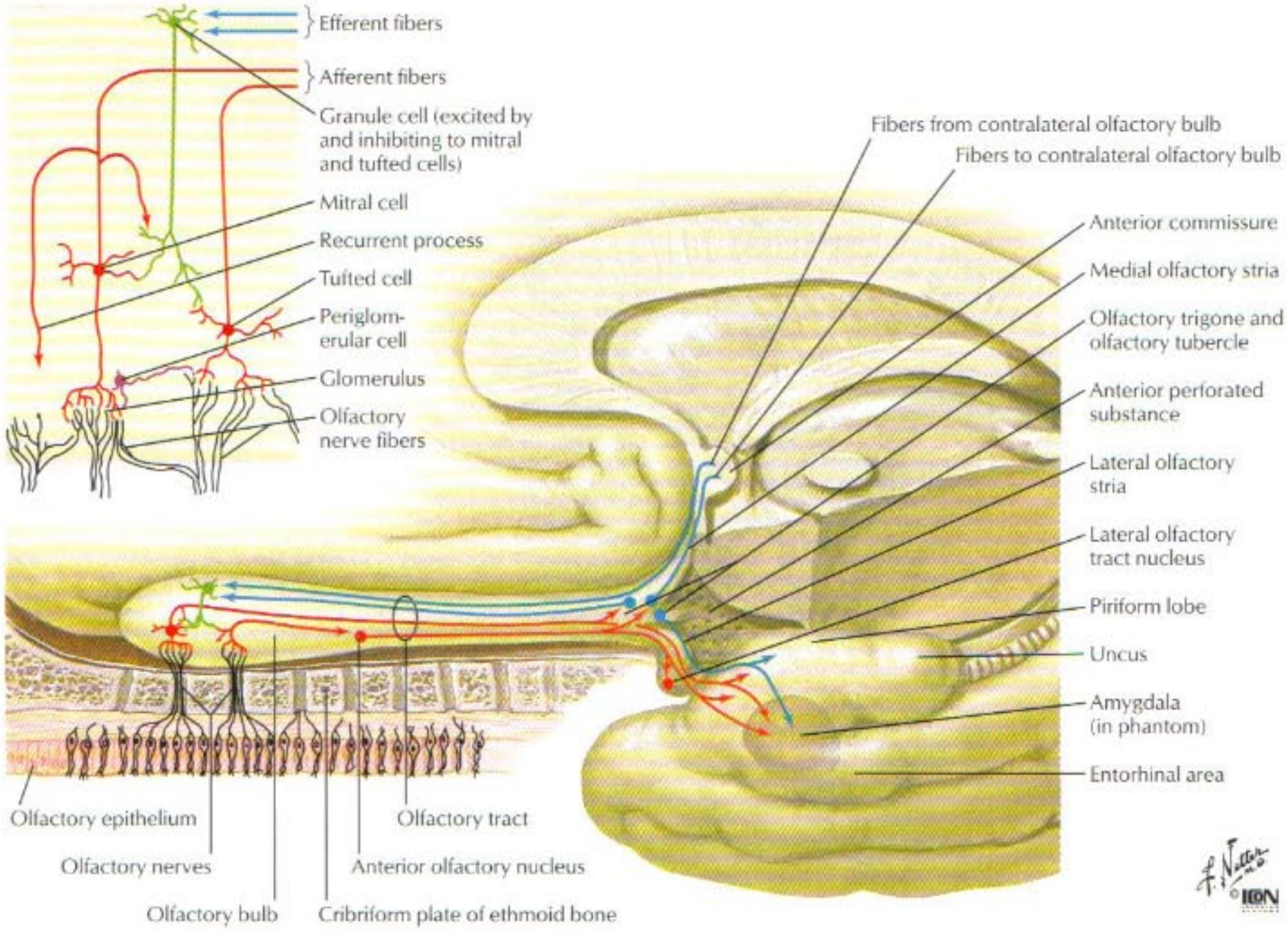
Efferent fibers
Afferent fibers
Granule cell (excited by and inhibiting to mitral and tufted cells)
Mitral cell
Recurrent process
Tufted cell
Periglomerular cell
Glomerulus
Olfactory nerve fibers
Fibers from contralateral olfactory bulb
Fibers to contralateral olfactory bulb
Anterior commissure
Medial olfactory stria
Olfactory trigone and olfactory tubercle
Anterior perforated substance
Lateral olfactory stria
Lateral olfactory tract nucleus
Piriform lobe
Uncus
Amygdala (in phantom)
Entorhinal area
Olfactory epithelium
Olfactory nerves
Olfactory bulb
Olfactory tract
Anterior olfactory nucleus
Cribriform plate of ethmoid bone
F. Netter
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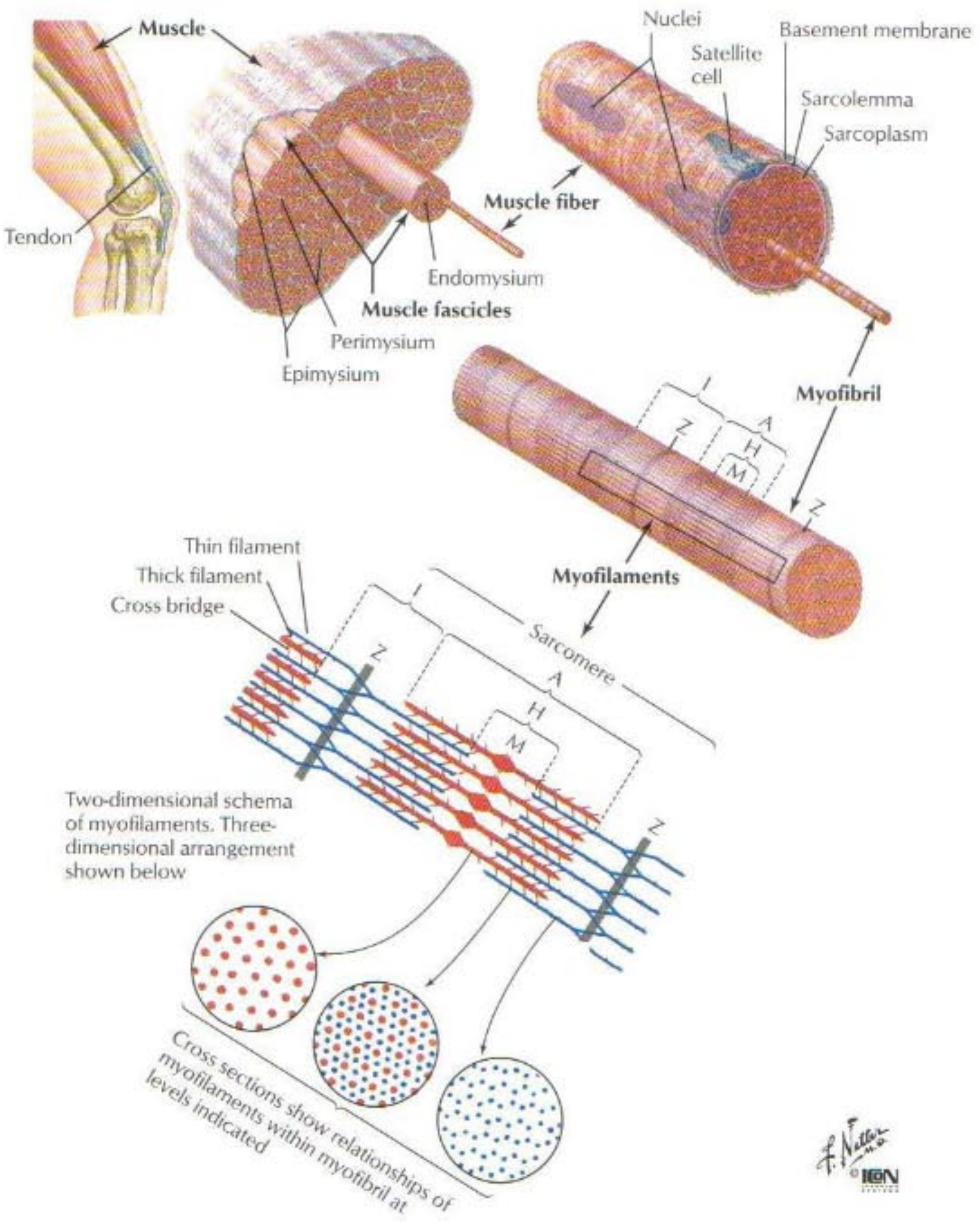
FIGURE 2.41 OLFACTORY PATHWAY

Olfactory stimuli are detected by the nerve fibers of the olfactory epithelium and conveyed to the olfactory bulb (detailed local circuitry shown in upper left panel). Integrated signals pass along the olfactory tract and centrally diverge to pass to the anterior commissure (some efferent projections course to the contralateral olfactory bulb, blue lines) or terminate in the ipsilateral olfactory trigone (olfactory tubercle). Axons then project to the primary olfactory cortex (piriform cortex), entorhinal cortex, and amygdala.


Muscle
Tendon
Nuclei
Satellite cell
Basement membrane
Sarcolemma
Sarcoplasm
Muscle fiber
Endomysium
Muscle fascicles
Perimysium
Epimysium
Myofibril
I
Z
A
H
M
Z
Myofilaments
Thin filament
Thick filament
Cross bridge
I
Z
Sarcomere
A
H
M
Z
F. Netter M.D.
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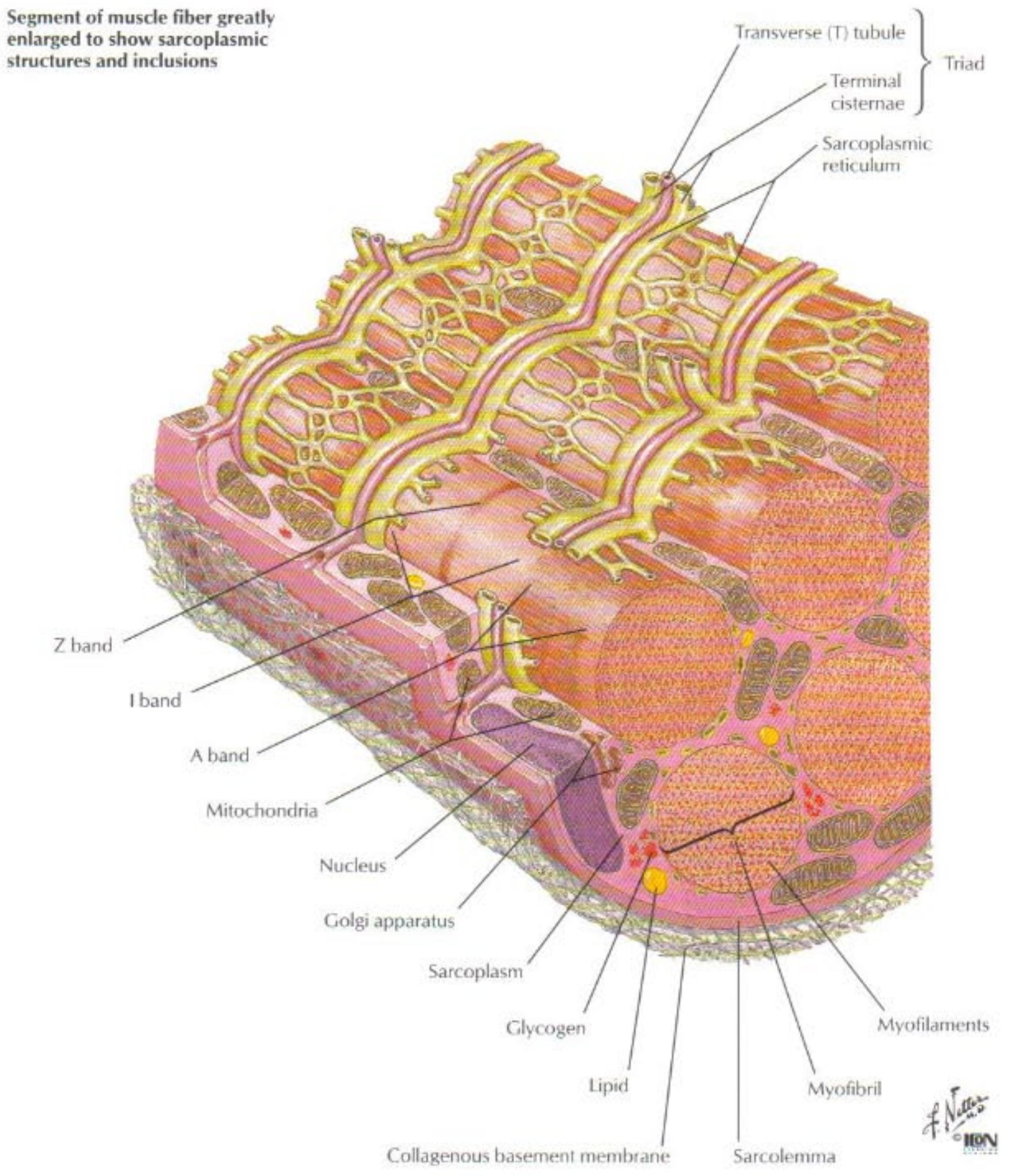
Two-dimensional schema of myofilaments. Three-dimensional arrangement shown below

Cross sections show relationships of myofilaments within myofibril at levels indicated

FIGURE 3.1 ORGANIZATION OF SKELETAL MUSCLE

Skeletal muscle is specialized for voluntary movement. The muscle fiber is a multinucleated cell that contains the contractile elements, called myofilaments. The myofilaments are organized as myofibrils within the fiber. Groups of muscle fibers are organized into muscle fascicles, which in turn are grouped to form a muscle. The regular arrangement of the myofibrils gives skeletal muscle a striated appearance under the microscope.



Segment of muscle fiber greatly enlarged to show sarcoplasmic structures and inclusions

Transverse (T) tubule
Terminal cisternae
Triad
Sarcoplasmic reticulum
Z band
I band
A band
Mitochondria
Nucleus
Golgi apparatus
Sarcoplasm
Glycogen
Lipid
Collagenous basement membrane
Sarcolemma
Myofibril
Myofilaments
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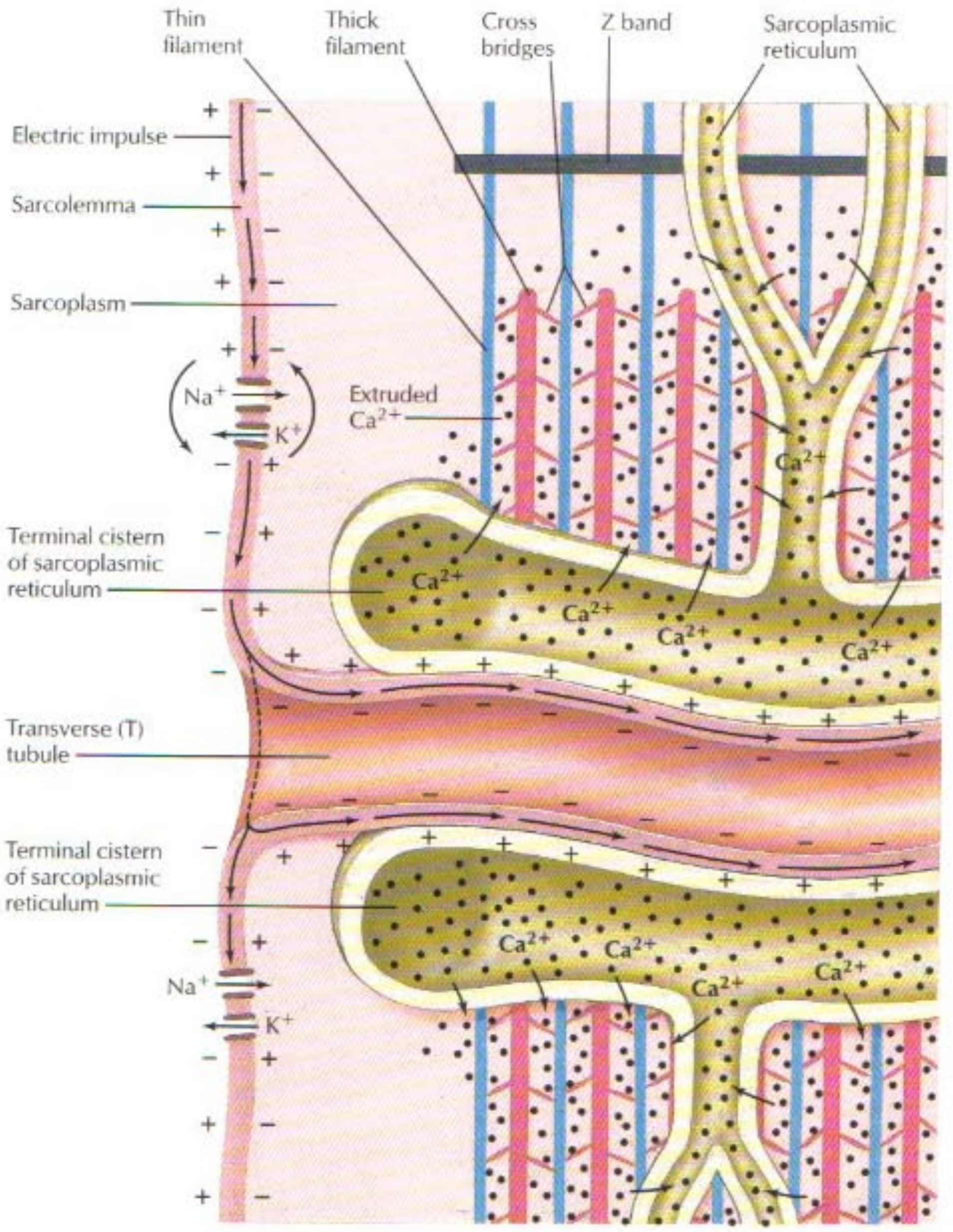
FIGURE 3.2 SARCOPLASMIC RETICULUM

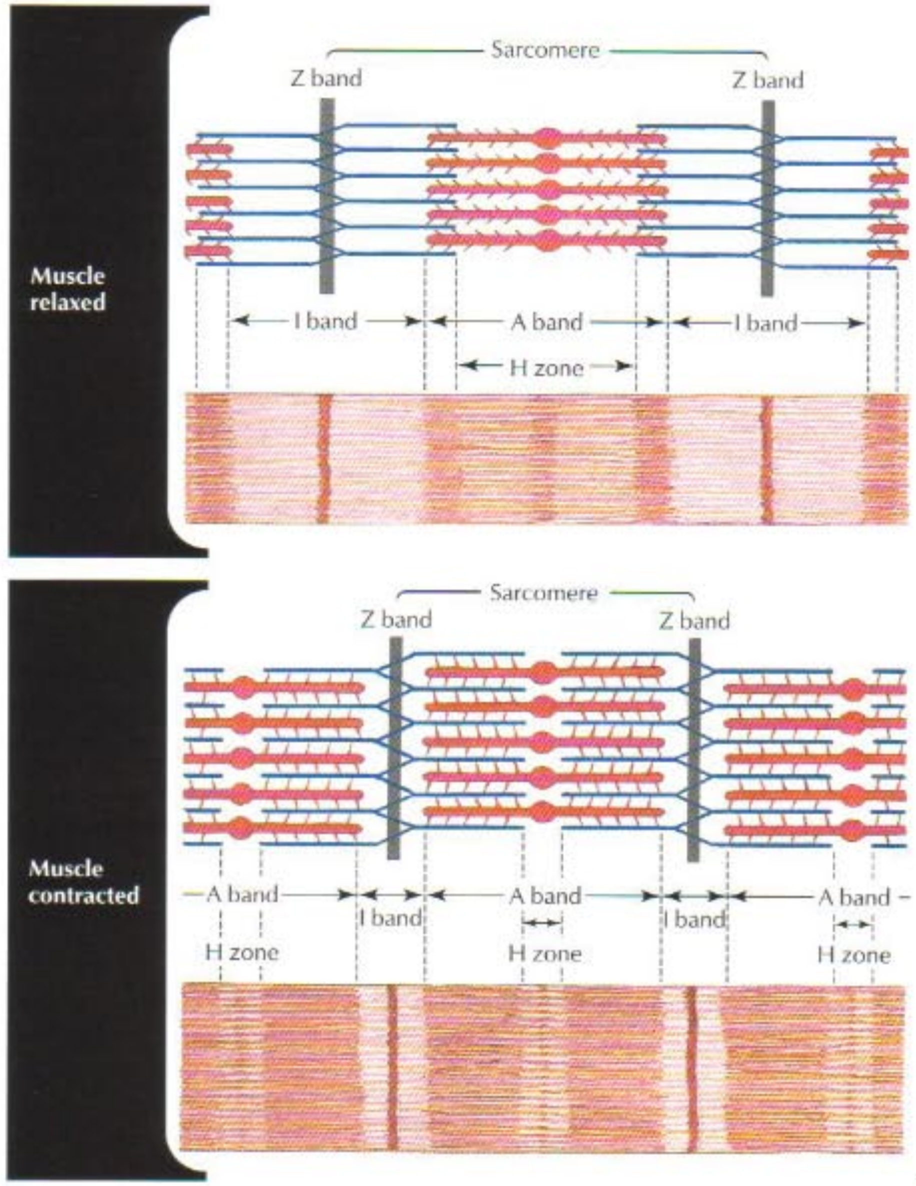
The sarcoplasmic reticulum forms an elaborate network within the cell and is the storage site for intracellular Ca^{2+}. The sarcoplasmic reticulum contains Ca^{2+} channels, Ca^{2+}-ATPase, and the low-affinity Ca^{2+}-binding protein calsequestrin. Transverse tubules (T tubules) invaginate from the sarcolemma (plasma membrane) and associate with two terminal cisternae of the sarcoplasmic reticulum (triad). Depolarization of the muscle sarcolemma travels down the T tubules and causes Ca^{2+} release from the sarcoplasmic reticulum (see Figure 3.3).


Thin filament
Thick filament
Cross bridges
Z band
Sarcoplasmic reticulum
Electric impulse
Sarcolemma
Sarcoplasm
Na^+
K^+
Extruded Ca^{2+}
Terminal cistern of sarcoplasmic reticulum
Ca^{2+}
Transverse (T) tubule
Terminal cistern of sarcoplasmic reticulum
Na^+
K^+

Electric impulse traveling along muscle cell membrane (sarcolemma) from motor endplate (neuromuscular junction) and then along transverse tubules affects sarcoplasmic reticulum, causing extrusion of Ca^{2+} to initiate contraction by "rowing" action of cross bridges, sliding filaments past one another

FIGURE 3.3 EXCITATION-CONTRACTION COUPLING

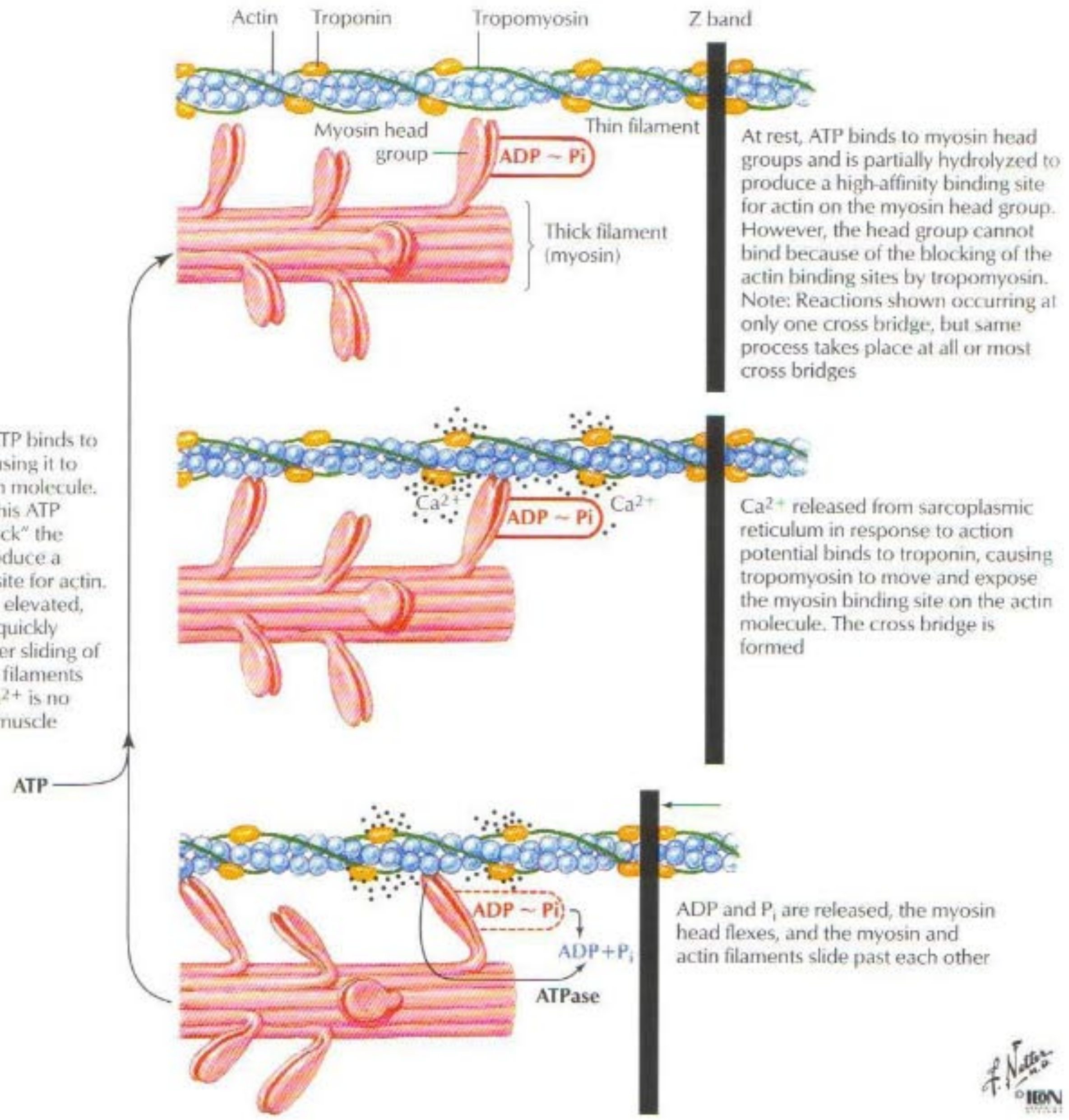
Impulses from motor neurons release acetylcholine (ACh) at the neuromuscular junction. The ACh receptor on the plasma membrane of the muscle fiber is a cation channel that opens when it binds ACh. As extracellular Na^+ enters the cell through the cation channel, the membrane depolarizes and an action potential is generated. The action potential spreads across the fiber and travels down specialized invaginations called *transverse* (T) *tubules*. The T tubules are in close apposition to the terminal cisternae of the sarcoplasmic reticulum (SR), and the spreading wave of depolarization along the T tubule causes Ca^{2+} release from the SR. Other regions of the SR also contain Ca^{2+}-ATPase, which serves to rapidly reaccumulate the released Ca^{2+} and end the contraction.


Muscle relaxed
Sarcomere
Z band
Z band
I band
A band
I band
H zone
Muscle contracted
Sarcomere
Z band
Z band
A band
I band
A band
I band
A band
H zone
H zone
H zone

During muscle contraction, thin filaments of each myofibril slide deeply between thick filaments, bringing Z bands closer together and shortening sarcomeres. A bands remain same width, but I bands narrowed. H zones also narrowed or disappear as thin filaments encroach upon them. Myofibrils, and consequently muscle fibers (muscle cells), fascicles, and muscle as whole grow thicker. During relaxation, reverse occurs

FIGURE 3.4 MUSCLE CONTRACTION AND RELAXATION

The sliding of the actin and myosin filaments past one another results in contraction. This sliding action is the result of the cyclical binding (cross-bridge formation) of actin and myosin.



At rest, ATP binds to myosin head groups and is partially hydrolyzed to produce a high-affinity binding site for actin on the myosin head group. However, the head group cannot bind because of the blocking of the actin binding sites by tropomyosin. Note: Reactions shown occurring at only one cross bridge, but same process takes place at all or most cross bridges

Ca^{2+} released from sarcoplasmic reticulum in response to action potential binds to troponin, causing tropomyosin to move and expose the myosin binding site on the actin molecule. The cross bridge is formed

ADP and P_i are released, the myosin head flexes, and the myosin and actin filaments slide past each other

A new molecule of ATP binds to the myosin head, causing it to release from the actin molecule. Partial hydrolysis of this ATP (ADP ~ Pi) will "recock" the myosin head and produce a high-affinity binding site for actin. If Ca^{2+} levels are still elevated, the cross bridge will quickly reform, causing further sliding of the actin and myosin filaments past each other. If Ca^{2+} is no longer elevated, the muscle relaxes

FIGURE 3.5 BIOCHEMICAL MECHANICS OF MUSCLE CONTRACTION

The contraction of the myofilaments results from the interaction of actin and myosin. In the resting state, myosin is prevented from interacting with actin because the regulatory protein tropomyosin overlies the myosin-binding sites on the actin filament. When Ca^{2+} is released from the SR, it binds to another regulatory protein, troponin. Troponin is closely associated with tropomyosin, and when it binds Ca^{2+}, it undergoes an conformational change that moves the tropomyosin and exposes the myosin-binding sites on the actin filament.

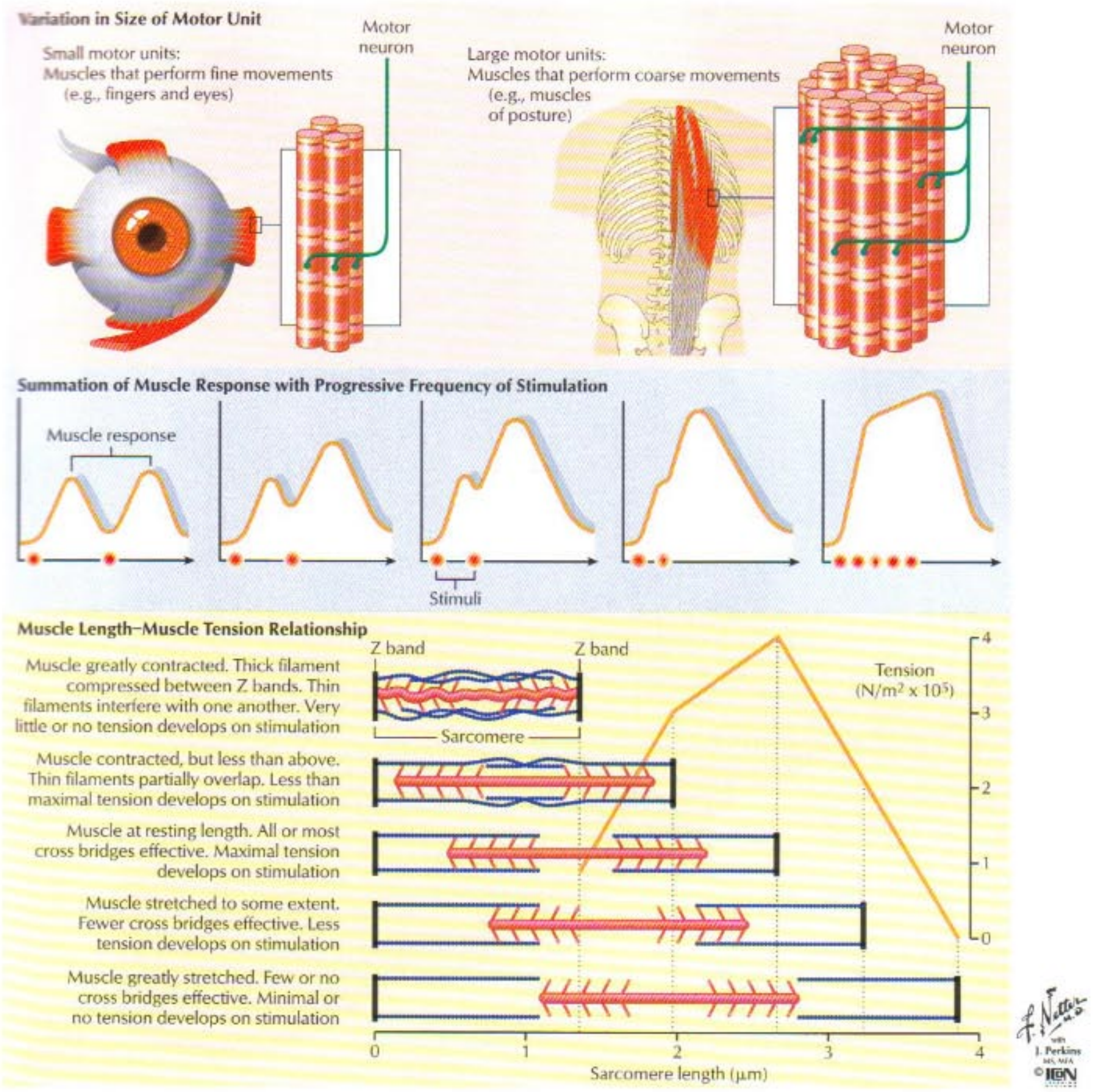

Variation in Size of Motor Unit
Small motor units:
Muscles that perform fine movements
(e.g., fingers and eyes)
Motor neuron
Large motor units:
Muscles that perform coarse movements
(e.g., muscles of posture)
Motor neuron
Summation of Muscle Response with Progressive Frequency of Stimulation
Muscle response
Stimuli
Muscle Length–Muscle Tension Relationship
Muscle greatly contracted. Thick filament compressed between Z bands. Thin filaments interfere with one another. Very little or no tension develops on stimulation
Muscle contracted, but less than above. Thin filaments partially overlap. Less than maximal tension develops on stimulation
Muscle at resting length. All or most cross bridges effective. Maximal tension develops on stimulation
Muscle stretched to some extent. Fewer cross bridges effective. Less tension develops on stimulation
Muscle greatly stretched. Few or no cross bridges effective. Minimal or no tension develops on stimulation
Z band
Z band
Sarcomere
Tension
(N/m² x 10⁵)
4
3
2
1
0
0
1
2
3
4
Sarcomere length (µm)
J. Perkins
MS, MFA
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FIGURE 3.6 GRADING OF MUSCLE TENSION AND LENGTH-TENSION RELATIONSHIP

The force or tension generated by skeletal muscle can vary by several mechanisms. First, more motor units can be recruited. As shown in the upper panel, a motor unit represents all the muscle fibers innervated by a single motor neuron. The firing of more motor neurons will result in the contraction of a larger number of motor units and thereby generate more tension by the muscle. Second, the frequency of stimulation of a single muscle fiber can increase the tension developed by that fiber. This process, called summation, is shown in the middle panel and results from the sustained elevation of intracellular $[\mathrm{Ca}^{2+}]$ that results from high-frequency stimulation. Finally, the tension generated by a single twitch varies as a function of sarcomere length. As shown in the lower panel, the degree of overlap of the thin and thick filaments varies as a function of sarcomere length. This in turn affects the number of cross bridges formed and thus tension developed.

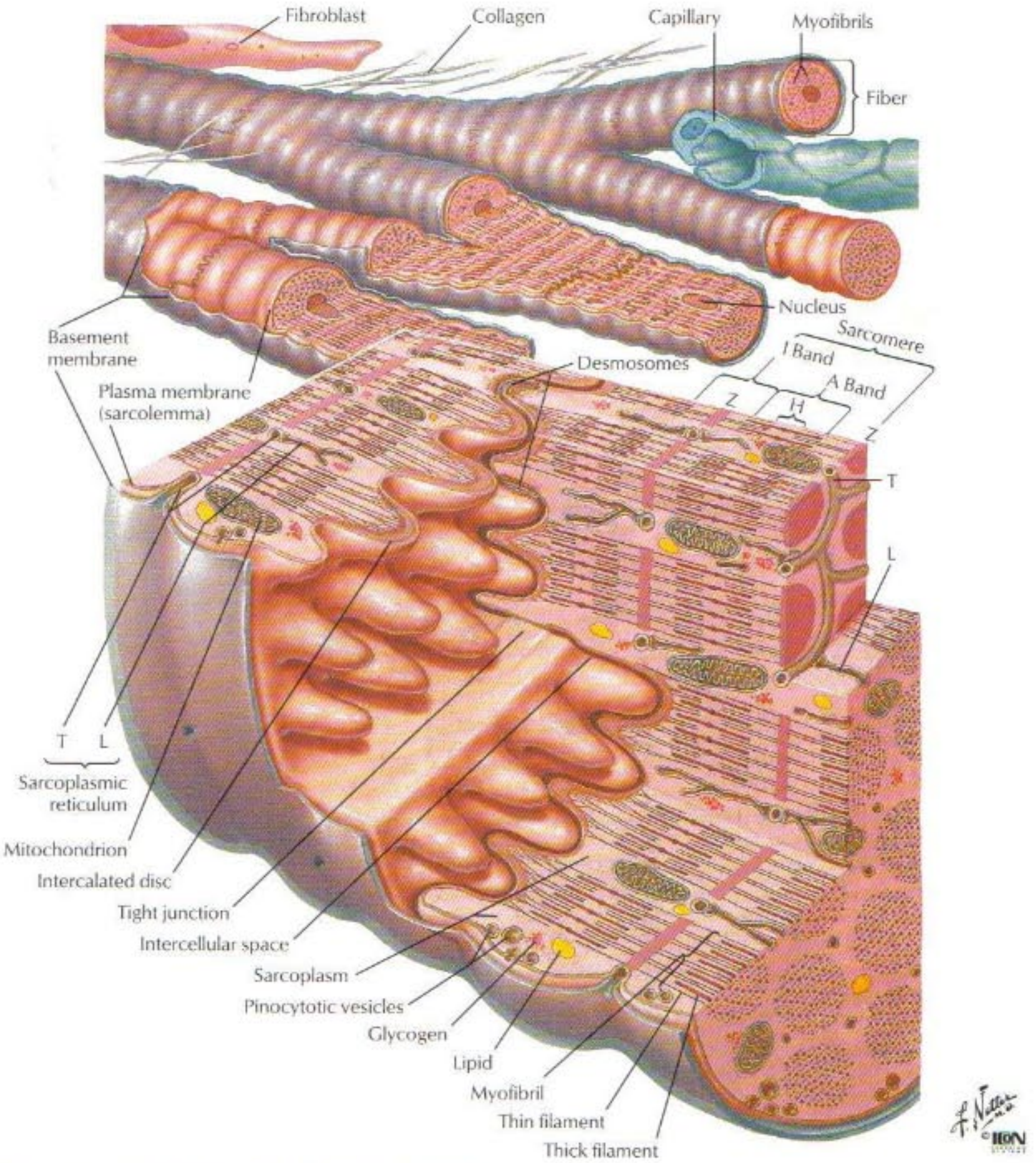
Fibroblast
Collagen
Capillary
Myofibrils
Fiber
Nucleus
Sarcomere
I Band
A Band
Z
H
Z
T
L
Desmosomes
Basement membrane
Plasma membrane (sarcolemma)
T
L
Sarcoplasmic reticulum
Mitochondrion
Intercalated disc
Tight junction
Intercellular space
Sarcoplasm
Pinocytotic vesicles
Glycogen
Lipid
Myofibril
Thin filament
Thick filament

Figure 3.7 Schema of Structure of Cardiac Muscle

Cardiac muscle, like skeletal muscle, is striated in appearance, reflecting the presence of the regularly arranged actin and myosin filaments. Cardiac muscle fibers are branched and electrically coupled to one another by gap junctions, which are located in the intercalated discs. The plasma membrane of the cardiac cell (myocyte) contains transverse (T) tubules like skeletal muscle. However, the sarcoplasmic reticulum is not as elaborate as in skeletal muscle, and dyads (rather than triads) are formed between the T tubules and sarcoplasmic reticulum.

Excitation-contraction coupling in cardiac muscle is similar to that of skeletal muscle, as is the process of cross-bridge formation and cycling. Although intracellular Ca^{2+} levels control contraction in both skeletal and cardiac muscle, there are some important differences. Skeletal muscle contraction is dependent on the release of Ca^{2+} from the sarcoplasmic reticulum, and changes in extracellular $[Ca^{2+}]$ do not appreciably alter the strength of the skeletal muscle contraction. In contrast, Ca^{2+} entry into the cardiac myocyte from the extracellular fluid is necessary for the release of Ca^{2+} from the sarcoplasmic reticulum, and removal of extracellular Ca^{2+} will decrease the force of contraction. The rate and force of contraction of cardiac myocytes can be increased by β-adrenergic agonists.

β-Adrenergic agonists do not have these effects on skeletal muscle.

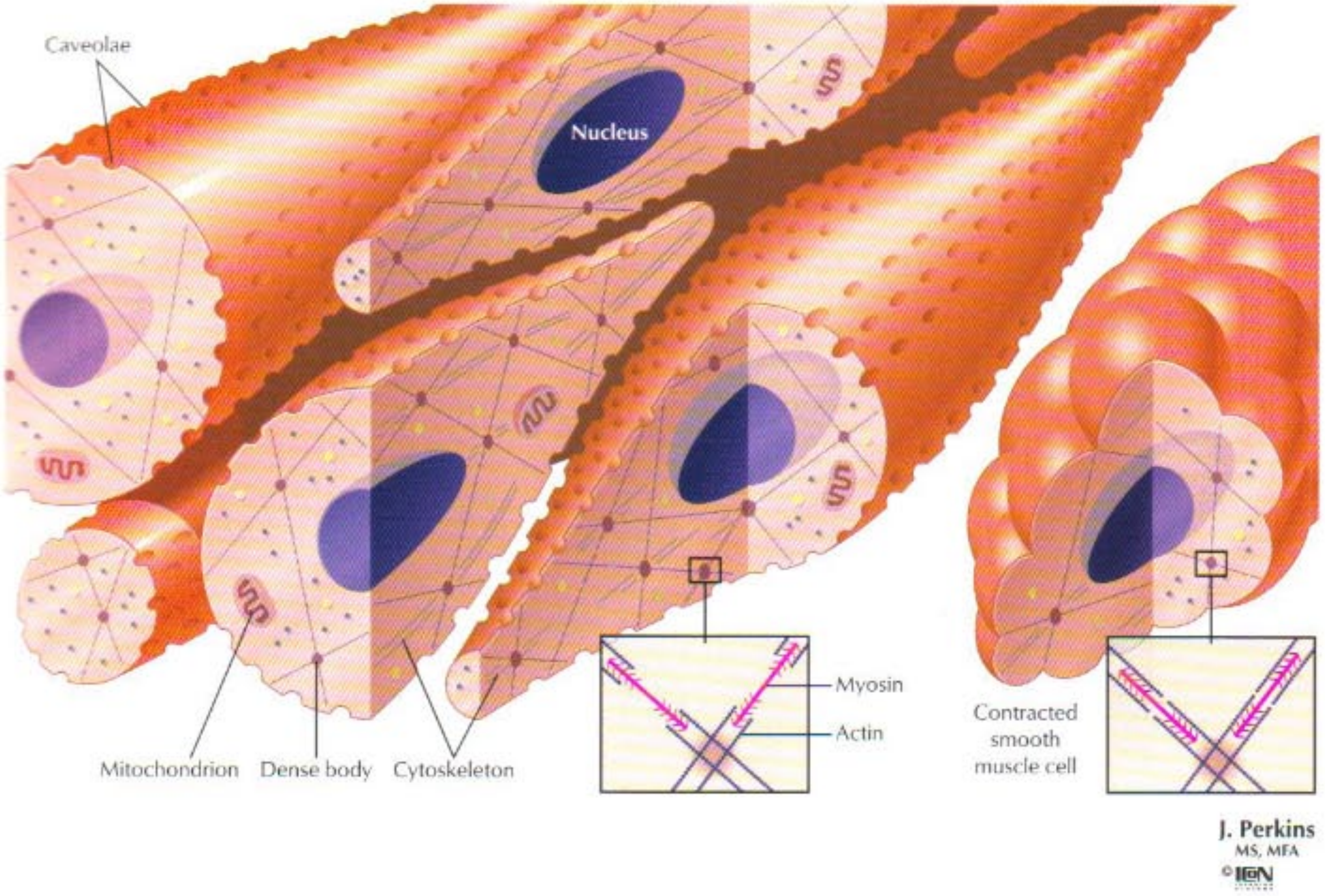
Caveolae
Nucleus
Mitochondrion
Dense body
Cytoskeleton
Myosin
Actin
Contracted smooth muscle cell
J. Perkins MS, MFA
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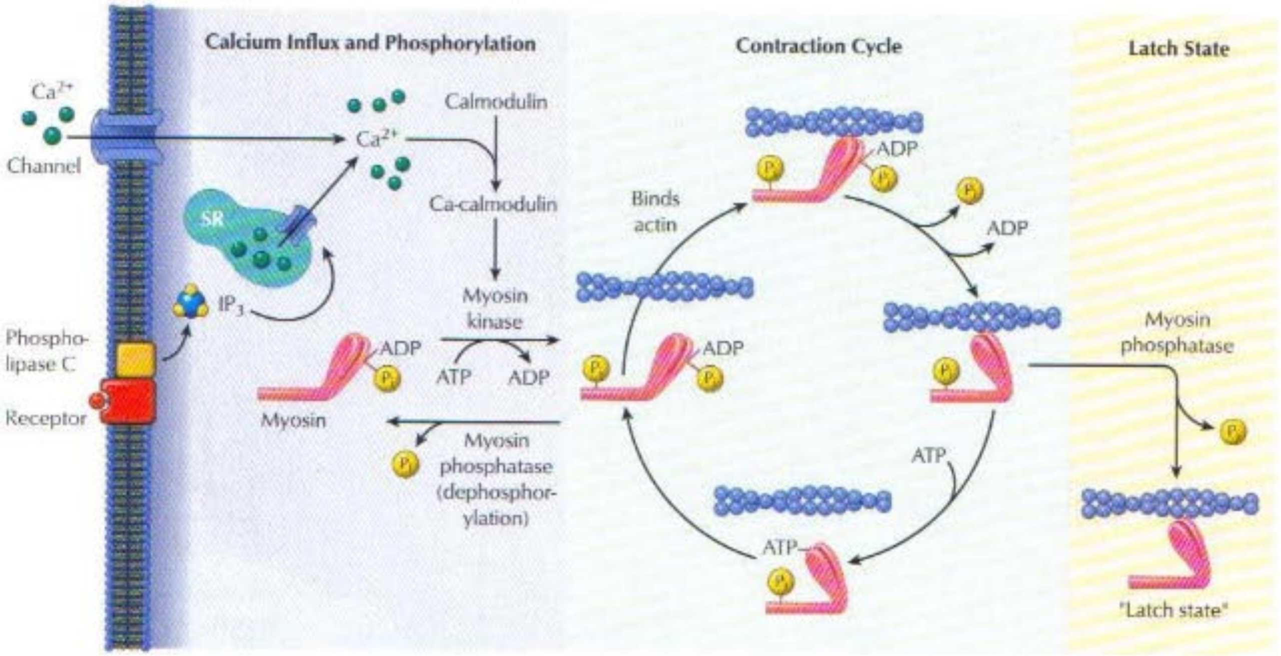
FIGURE 3.8 SMOOTH MUSCLE STRUCTURE

Myofibrils are not found in smooth muscle cells. Instead, actin filaments are anchored to the plasma membrane and to dense bodies within the cytoplasm. Myosin interaction with the actin filaments causes the cell to contract. Smooth muscle cells do not contain T tubules. Instead, caveolae serve a similar function and are a site for entry of extracellular Ca^{2+} into the cell. Smooth muscle serves a wide range of functions, even within the same organ, and is capable of changing its morphology as circumstances demand (e.g., hypertrophy, or in instances where the number of gap junctions changes).


Calcium Influx and Phosphorylation
Contraction Cycle
Latch State
Ca2+
Channel
Ca2+
Calmodulin
SR
Ca-calmodulin
IP3
Phospholipase C
Receptor
Myosin kinase
ADP
ATP
ADP
Myosin
Myosin phosphatase (dephosphorylation)
Binds actin
ADP
ADP
ADP
ATP
ATP
Myosin phosphatase
"Latch state"

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MS, MFA
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FIGURE 3.9 EXCITATION-CONTRACTION COUPLING OF SMOOTH MUSCLE

Both extracellular Ca^{2+} and Ca^{2+} release from the sarcoplasmic reticulum regulate smooth muscle contraction. At high intracellular $[Ca^{2+}]$, myosin light-chain kinase (myosin kinase) phosphorylates myosin, which allows actin and myosin to interact. The sliding of actin past myosin in the contraction phase is similar to that of skeletal muscle. As long as the intracellular $[Ca^{2+}]$ is high, the contraction cycle continues. Dephosphorylation of myosin by myosin phosphorylase when it is attached to actin slows the contraction cycle, leading to the latch state (i.e., tonic contraction without hydrolysis of ATP).

CHART 3.1 COMPARISION OF MUSCLE STRUCTURE AND FUNCTION

	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Structure			
Morphology	Long; cylindrical	Branched	Spindle or fusiform
Nuclei	Multiple; located peripherally	One (sometimes two); located centrally	One; located centrally
Sarcomere	Yes; striated pattern	Yes; striated pattern	No
T tubules	Yes; forms triad with sarcoplasmic reticulum	Yes; forms dyad with sarcoplasmic reticulum	No; caveolae
Electrical coupling of cells	No	Yes; intercalated discs contain gap junctions	Yes; gap junctions
Regeneration	Yes; via satellite cells	No	Yes
Mitosis	No	No	Yes
Physiology			
Extracellular Ca^{2+} required for contraction	No	Yes	Yes
Regulation of cross-bridge formation	Ca^{2+} binding to troponin	Ca^{2+} binding to troponin	Ca^{2+}-calmodulin activation of myosin kinase and phosphorylation of myosin
Control of contraction	Motor neurons	Autonomic nerves; β-adrenergic agonists	Autonomic nerves; hormones
Summation of twitches by increased stimulus frequency	Yes	No*	Yes
Tension varies with filament overlap	Yes	Yes	Yes

Major differences in structure and function of skeletal, cardiac, and smooth muscle are indicted.

*Cardiac muscle cannot be tetanized, but the force of contraction will increase at high stimulus frequency because of an increase in intracellular $[Ca^{2+}]$, a phenomenon termed "Treppe."

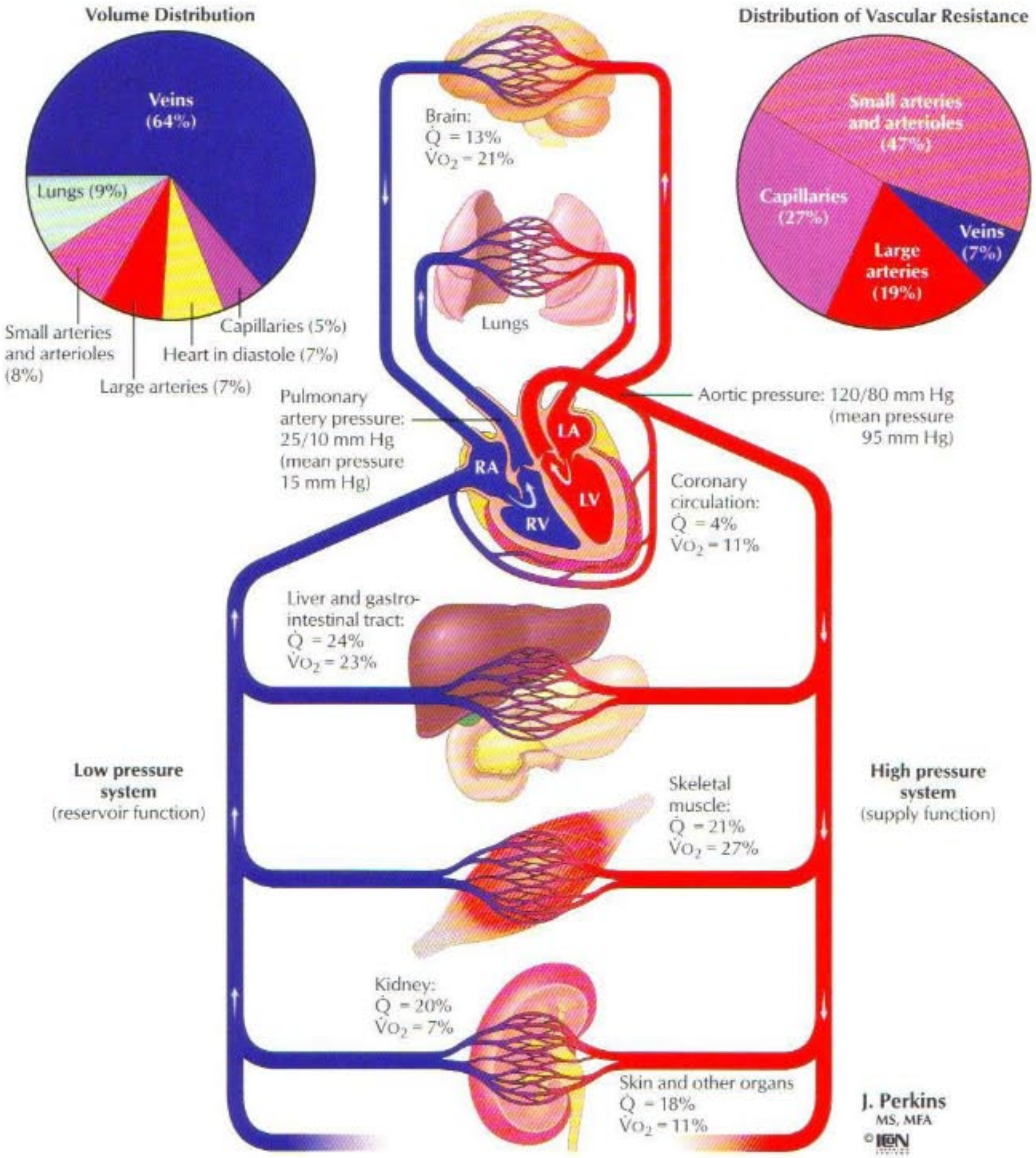
Volume Distribution
Veins (64%)
Lungs (9%)
Small arteries and arterioles (8%)
Large arteries (7%)
Heart in diastole (7%)
Capillaries (5%)
Distribution of Vascular Resistance
Small arteries and arterioles (47%)
Capillaries (27%)
Large arteries (19%)
Veins (7%)
Brain: $\dot{Q}$ = 13% $\dot{V}O_2$ = 21%
Lungs
Pulmonary artery pressure: 25/10 mm Hg (mean pressure 15 mm Hg)
Aortic pressure: 120/80 mm Hg (mean pressure 95 mm Hg)
RA
LA
RV
LV
Coronary circulation: $\dot{Q}$ = 4% $\dot{V}O_2$ = 11%
Liver and gastrointestinal tract: $\dot{Q}$ = 24% $\dot{V}O_2$ = 23%
Low pressure system (reservoir function)
High pressure system (supply function)
Skeletal muscle: $\dot{Q}$ = 21% $\dot{V}O_2$ = 27%
Kidney: $\dot{Q}$ = 20% $\dot{V}O_2$ = 7%
Skin and other organs $\dot{Q}$ = 18% $\dot{V}O_2$ = 11%
J. Perkins MS, MFA
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FIGURE 4.1 CARDIOVASCULAR SYSTEM OVERVIEW

The cardiovascular system consists of the heart, which pumps blood into the pulmonary circulation for the exchange of O_2 and CO_2 and into the systemic circulation to supply all other tissues of the body. At rest, cardiac output is approximately 5 L/min in both the pulmonary and systemic circulations. The amount of blood flow (Q) (as a percentage of cardiac output) and relative percentage of oxygen utilization per minute (Vo_2) to various organ systems is shown for the resting state. The systemic circulation is arranged in a parallel fashion (brain, heart, gastrointestinal tract, etc.). Based on metabolic need and demand, both Q and Vo_2 may be adjusted. At any one time, most of the blood volume resides in the veins (64%) and is returned to the right side of the heart. Vascular resistance is primarily a function of the small muscular arteries and arterioles.

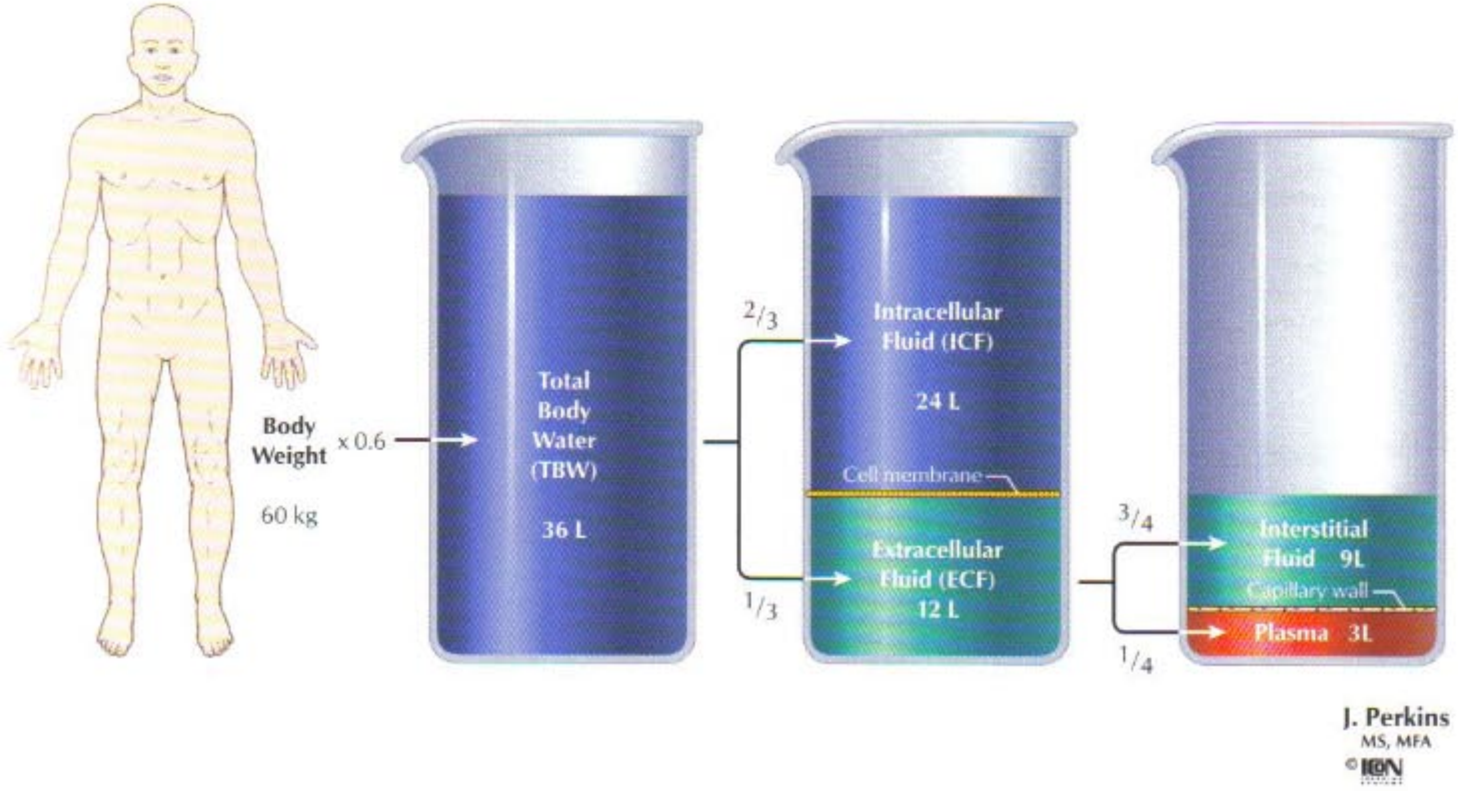
Body Weight
60 kg
× 0.6
Total Body Water (TBW)
36 L
2/3
Intracellular Fluid (ICF)
24 L
Cell membrane
1/3
Extracellular Fluid (ECF)
12 L
3/4
Interstitial Fluid 9L
Capillary wall
1/4
Plasma 3L
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FIGURE 4.2 BODY FLUID COMPARTMENTS

Total body water (calculated for a 60-kg individual) is divided by the plasma membrane of cells into two compartments: intracellular fluid and extracellular fluid. The capillary wall subdivides the extracellular fluid into plasma (within blood vessels) and interstitial fluid. The interstitial fluid includes not only the fluid surrounding cells but also fluid in bone and dense connective tissue.

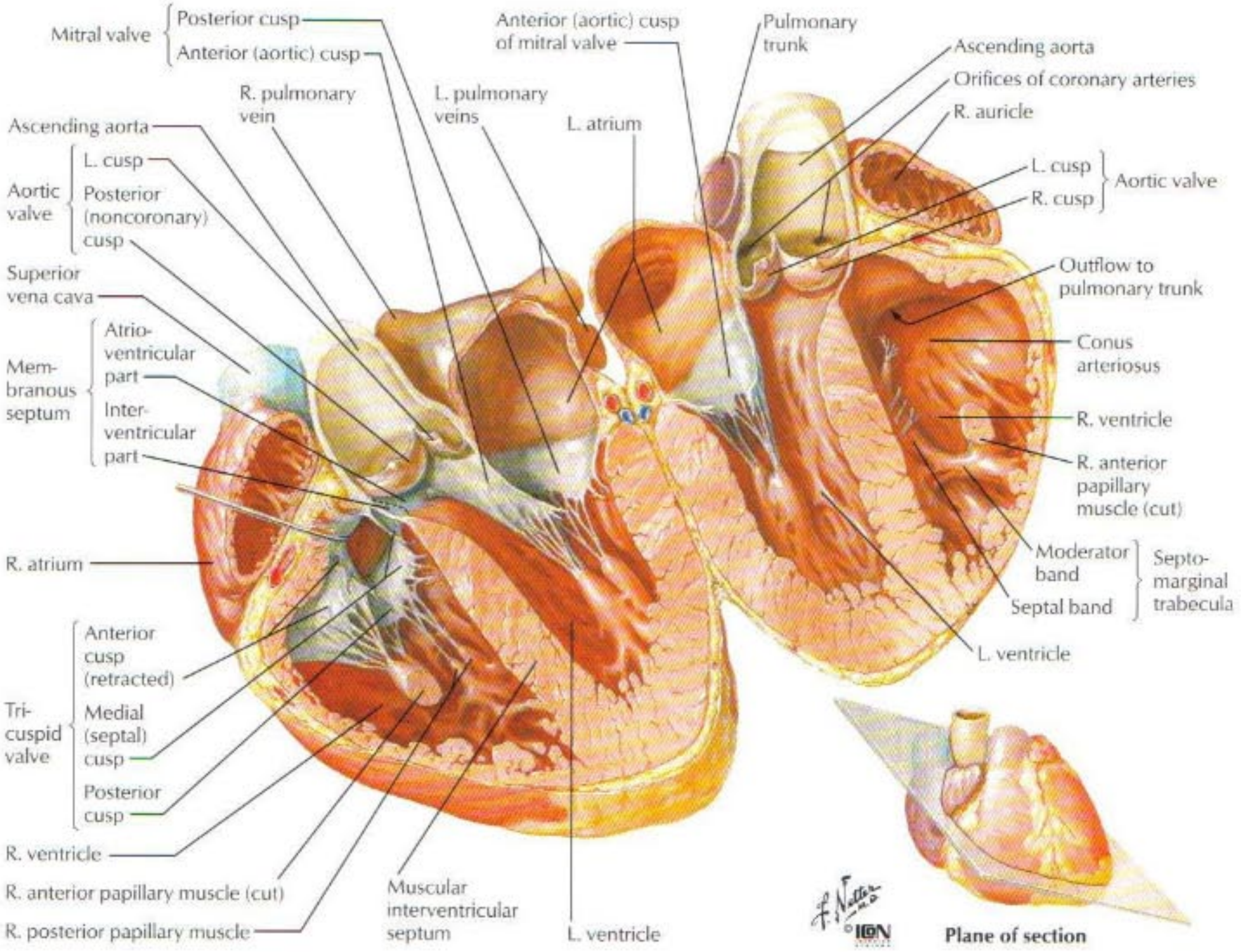

Mitral valve
Posterior cusp
Anterior (aortic) cusp
R. pulmonary vein
L. pulmonary veins
Anterior (aortic) cusp of mitral valve
L. atrium
Pulmonary trunk
Ascending aorta
Orifices of coronary arteries
R. auricle
L. cusp
R. cusp
Aortic valve
Outflow to pulmonary trunk
Conus arteriosus
R. ventricle
R. anterior papillary muscle (cut)
Moderator band
Septal band
Septo-marginal trabecula
L. ventricle
Ascending aorta
Aortic valve
L. cusp
Posterior (noncoronary) cusp
Superior vena cava
Membranous septum
Atrioventricular part
Interventricular part
R. atrium
Tricuspid valve
Anterior cusp (retracted)
Medial (septal) cusp
Posterior cusp
R. ventricle
R. anterior papillary muscle (cut)
R. posterior papillary muscle
Muscular interventricular septum
L. ventricle
Plane of section

FIGURE 4.3 STRUCTURE OF HEART

This interior view of the heart shows its four chambers, valves, and septa. The right side of the heart receives blood from the systemic circulation and pumps it into the pulmonary circulation. The left side of the heart receives blood returning from the pulmonary circulation and pumps it into the systemic circulation. The work of the left ventricle is significantly greater than that of the right ventricle, and its walls are correspondingly much thicker.

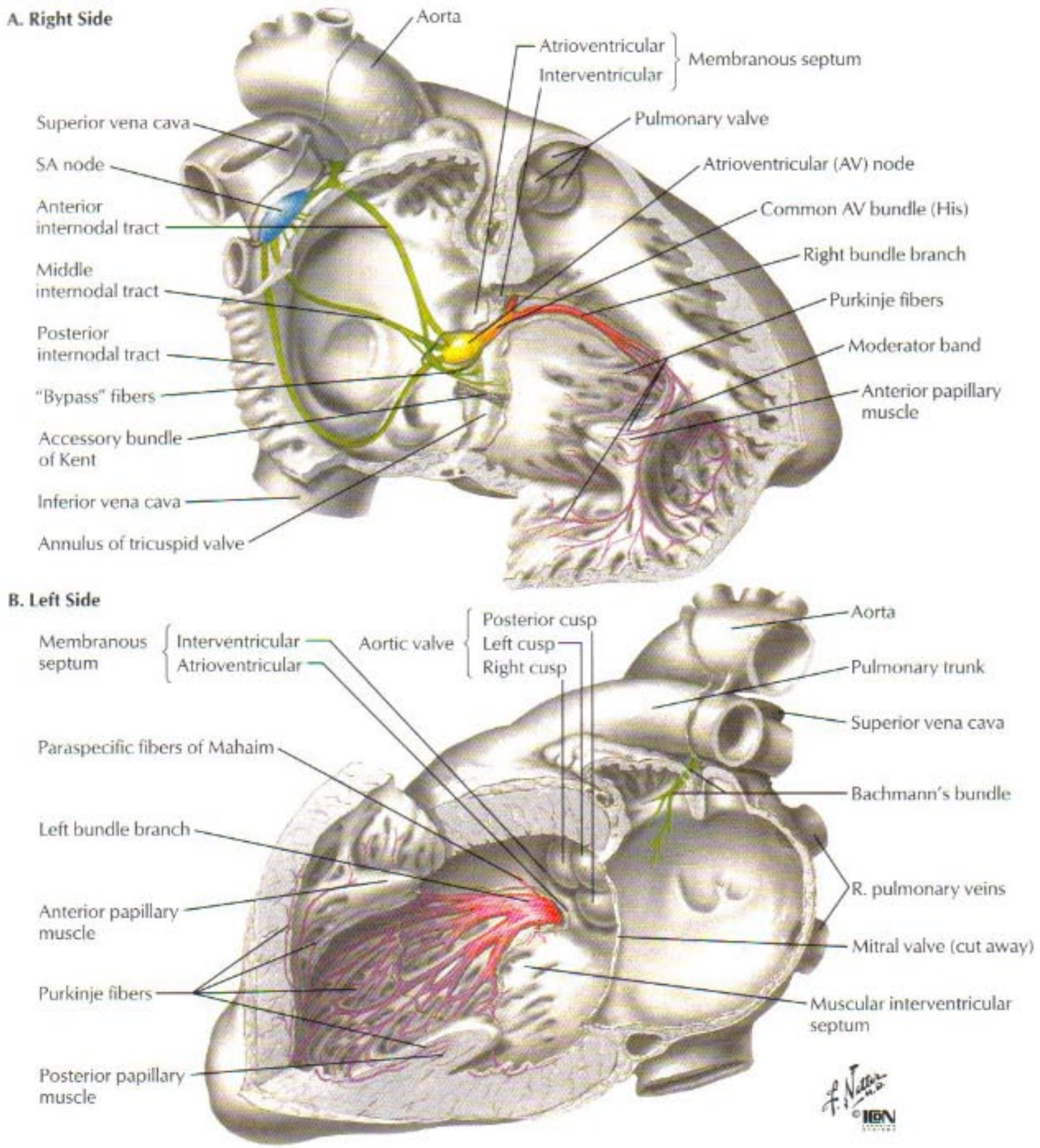

A. Right Side
Aorta
Atrioventricular
Interventricular
Membranous septum
Pulmonary valve
Superior vena cava
SA node
Atrioventricular (AV) node
Anterior internodal tract
Common AV bundle (His)
Right bundle branch
Middle internodal tract
Purkinje fibers
Posterior internodal tract
Moderator band
"Bypass" fibers
Anterior papillary muscle
Accessory bundle of Kent
Inferior vena cava
Annulus of tricuspid valve
B. Left Side
Membranous septum
Interventricular
Atrioventricular
Aortic valve
Posterior cusp
Left cusp
Right cusp
Aorta
Pulmonary trunk
Superior vena cava
Paraspecific fibers of Mahaim
Bachmann's bundle
Left bundle branch
R. pulmonary veins
Anterior papillary muscle
Mitral valve (cut away)
Purkinje fibers
Muscular interventricular septum
Posterior papillary muscle

FIGURE 4.4 ANATOMY OF THE SPECIALIZED CONDUCTION SYSTEM

Cardiac muscle of the heart exists in two forms: the contractile myocardium and specialized conducting cells that do not contract but do spread the wave of depolarization rapidly throughout the chambers of the heart. Action potentials are initiated in the sinoatrial (SA) node, which serves as the "pacemaker" of the heart. Impulses are conveyed to the atrioventricular (AV) node and then to the common AV bundle (of His). From here, the action potential spreads rapidly through the ventricles via the right and left bundle branches and Purkinje fiber system.

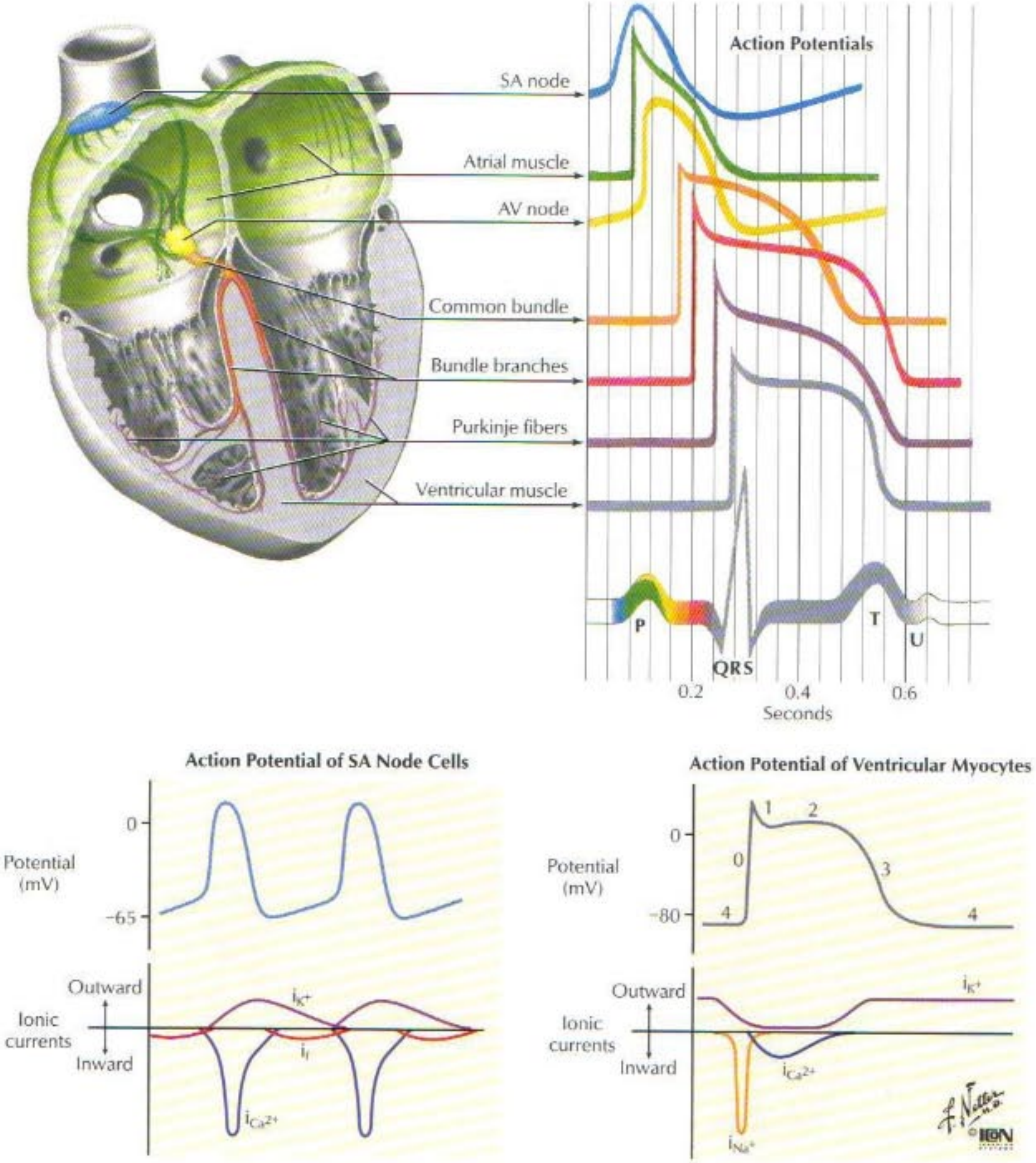
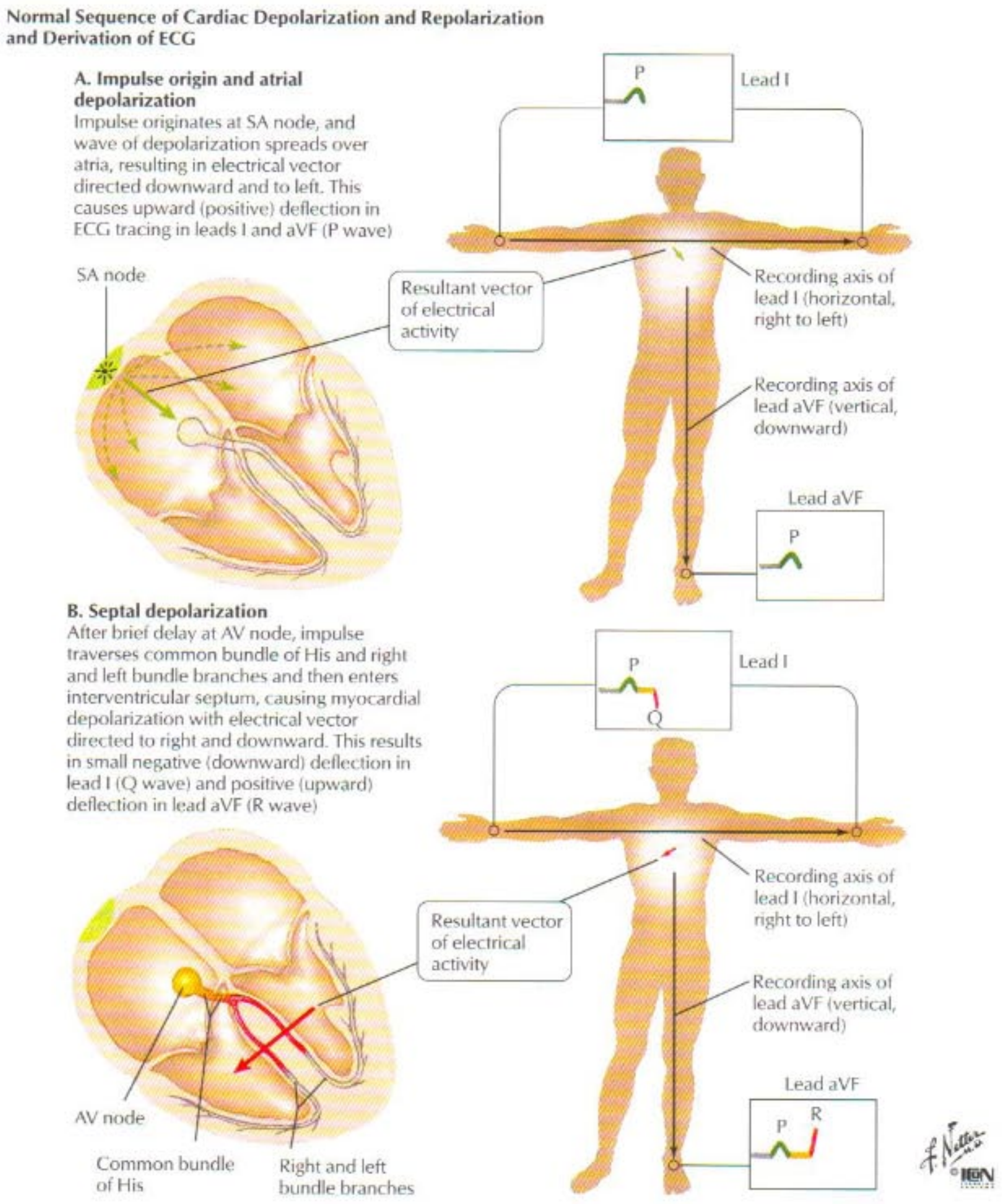

SA node
Atrial muscle
AV node
Common bundle
Bundle branches
Purkinje fibers
Ventricular muscle
Action Potentials
P
QRS
T
U
0.2
0.4
0.6
Seconds
Action Potential of SA Node Cells
Potential (mV)
0
-65
Outward
Ionic currents
Inward
i_{K^+}
i_f
$i_{Ca^{2+}}$
Action Potential of Ventricular Myocytes
Potential (mV)
0
-80
0
1
2
3
4
4
Outward
Ionic currents
Inward
i_{K^+}
$i_{Ca^{2+}}$
i_{Na^+}

FIGURE 4.5 ELECTRICAL ACTIVITY OF THE HEART

The normal pumping of blood through the chambers of the heart requires the precisely timed spread of action potentials through the heart's conduction system and the atrial and ventricular muscle. The rate of the heartbeat is set by spontaneously generated action potentials in the cells of the SA node. The frequency of SA node action potentials is regulated by the autonomic nervous system. Sympathetic stimulation of the SA node increases i_f (principally Na^+ current) and $i_{Ca^{2+}}$, which depolarizes the cell, and thereby increases the heart rate. Parasympathetic stimulation increases i_{K^+}, which hyperpolarizes the cell and thereby decreases the heart rate. The ventricular muscle action potential has a prolonged depolarization phase resulting from Ca^{2+} influx. This long plateau phase prevents tetany of cardiac muscle at very high heart rates.



Normal Sequence of Cardiac Depolarization and Repolarization and Derivation of ECG

A. Impulse origin and atrial depolarization
Impulse originates at SA node, and wave of depolarization spreads over atria, resulting in electrical vector directed downward and to left. This causes upward (positive) deflection in ECG tracing in leads I and aVF (P wave)

B. Septal depolarization
After brief delay at AV node, impulse traverses common bundle of His and right and left bundle branches and then enters interventricular septum, causing myocardial depolarization with electrical vector directed to right and downward. This results in small negative (downward) deflection in lead I (Q wave) and positive (upward) deflection in lead aVF (R wave)

P
Lead I
SA node
Resultant vector of electrical activity
Recording axis of lead I (horizontal, right to left)
Recording axis of lead aVF (vertical, downward)
Lead aVF
P
P
Lead I
Q
Resultant vector of electrical activity
Recording axis of lead I (horizontal, right to left)
Recording axis of lead aVF (vertical, downward)
Lead aVF
P
R
AV node
Common bundle of His
Right and left bundle branches

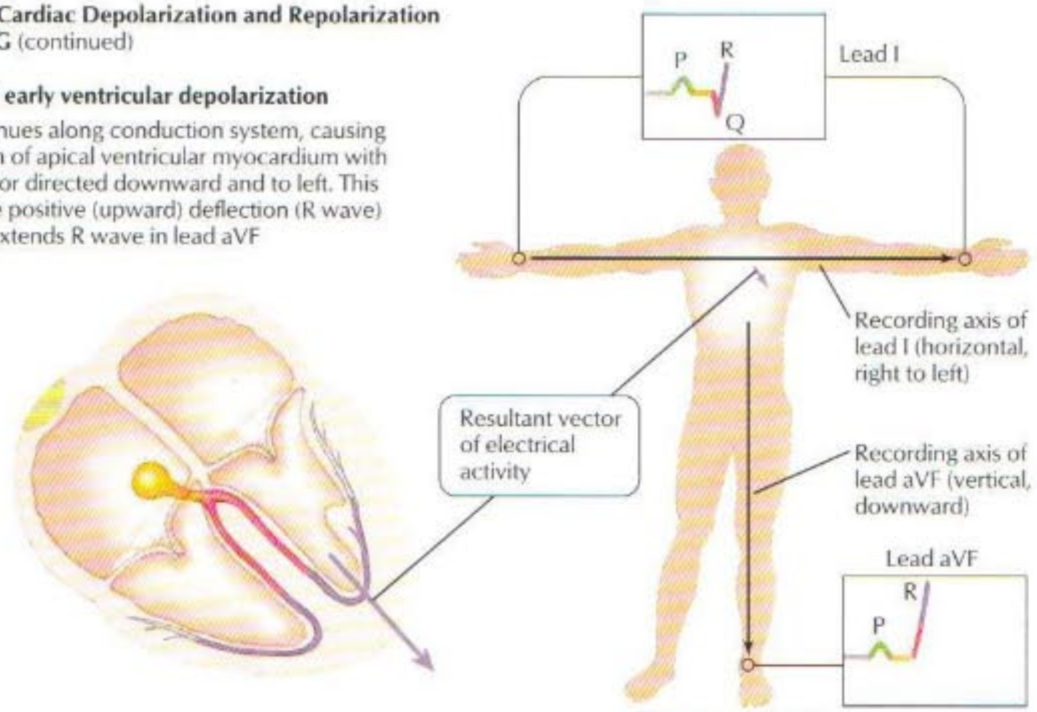
Figure 4.6 Cardiac Depolarization and Repolarization Part 1

The elements of the electrocardiogram (ECG) are shown in the next three figures. Beginning with the SA node (pacemaker), depolarization spreads over the atria, causing an upward deflection of the ECG tracing (P wave) (panel A). The delay at the AV node ensures that the ventricles will have ample time to fill, and then the impulse passes through the bundle of His and the bundle branches of the interventricular septum. The resulting depolarization of the myocardium of the septum yields the Q wave of the ECG tracing (panel B).

Normal Sequence of Cardiac Depolarization and Repolarization and Derivation of ECG (continued)

C. Apical and early ventricular depolarization

Impulse continues along conduction system, causing depolarization of apical ventricular myocardium with electrical vector directed downward and to left. This results in large positive (upward) deflection (R wave) in lead I and extends R wave in lead aVF


Lead I
P
R
Q
Recording axis of lead I (horizontal, right to left)
Resultant vector of electrical activity
Recording axis of lead aVF (vertical, downward)
Lead aVF
R
P

D. Late ventricular depolarization

As depolarization progresses over ventricles, vector shifts to become directed superiorly as well as to left, thus extending upward R wave in lead I and causing negative (downward) deflection (S wave) in lead aVF

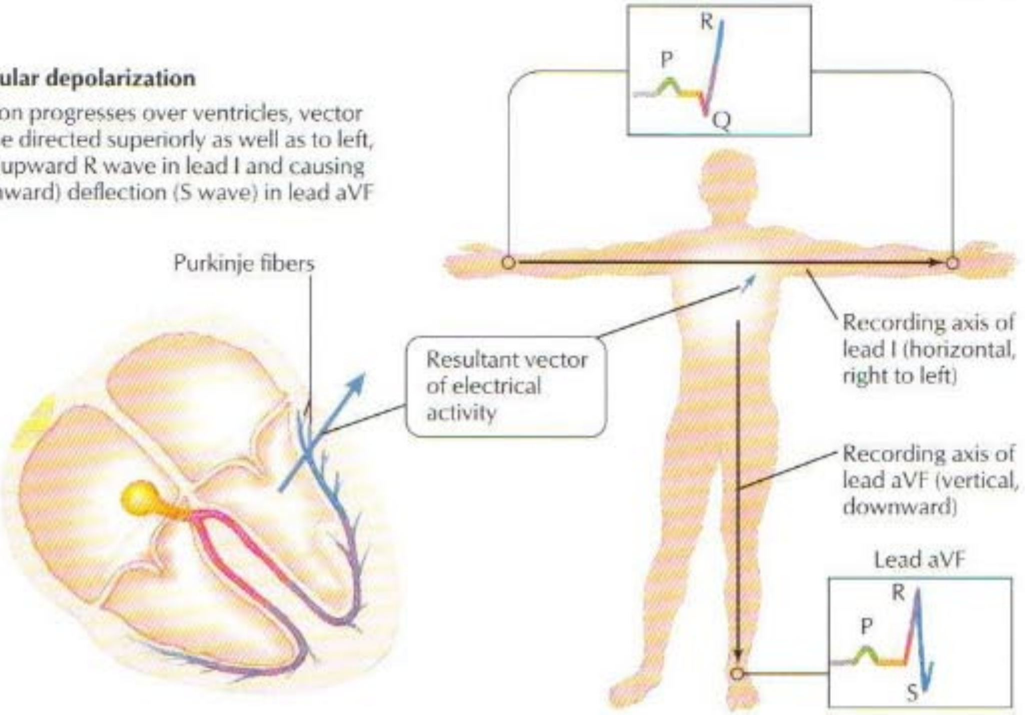
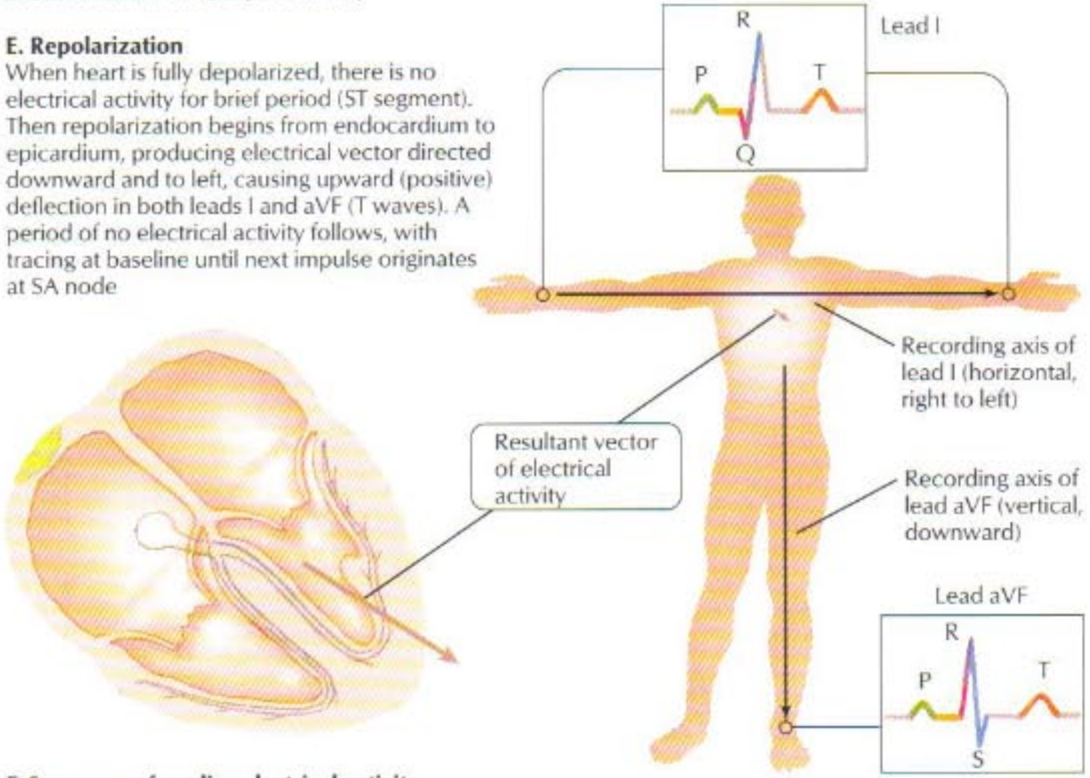

R
P
Q
Purkinje fibers
Resultant vector of electrical activity
Recording axis of lead I (horizontal, right to left)
Recording axis of lead aVF (vertical, downward)
Lead aVF
R
P
S

FIGURE 4.7 CARDIAC DEPOLARIZATION AND REPOLARIZATION PART 2

ECG continued. As the apex of the ventricles contracts, a large upward positive deflection of the tracing yields the R wave of the ECG (panel C). Then the wave of depolarization spreads through the ventricular walls, causing the S wave of the ECG tracing (panel D).

Normal Sequence of Cardiac Depolarization and Repolarization and Derivation of ECG (continued)

E. Repolarization
When heart is fully depolarized, there is no electrical activity for brief period (ST segment). Then repolarization begins from endocardium to epicardium, producing electrical vector directed downward and to left, causing upward (positive) deflection in both leads I and aVF (T waves). A period of no electrical activity follows, with tracing at baseline until next impulse originates at SA node


R
P
T
Q
Lead I
Recording axis of lead I (horizontal, right to left)
Resultant vector of electrical activity
Recording axis of lead aVF (vertical, downward)
Lead aVF
R
P
T
S

F. Summary of cardiac electrical activity

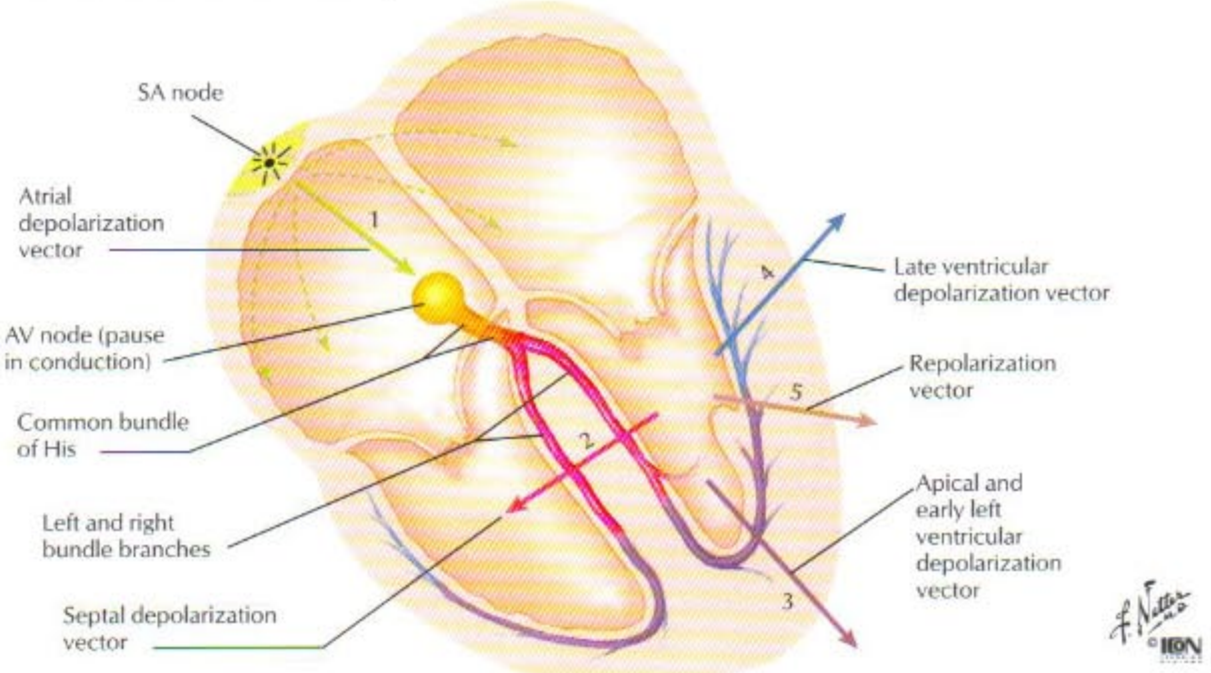

SA node
Atrial depolarization vector
1
AV node (pause in conduction)
Common bundle of His
Left and right bundle branches
Septal depolarization vector
2
4
Late ventricular depolarization vector
5
Repolarization vector
Apical and early left ventricular depolarization vector
3

FIGURE 4.8 CARDIAC DEPOLARIZATION AND REPOLARIZATION PART 3

ECG continued. Once fully depolarized, electrical activity ceases briefly (the ST segment of the tracing), and then repolarization begins, moving from the inner endocardium to the outer epicardium, generating the T wave of the ECG tracing (panel E). Panel F summarizes the sequence of events in myocardial depolarization and repolarization.

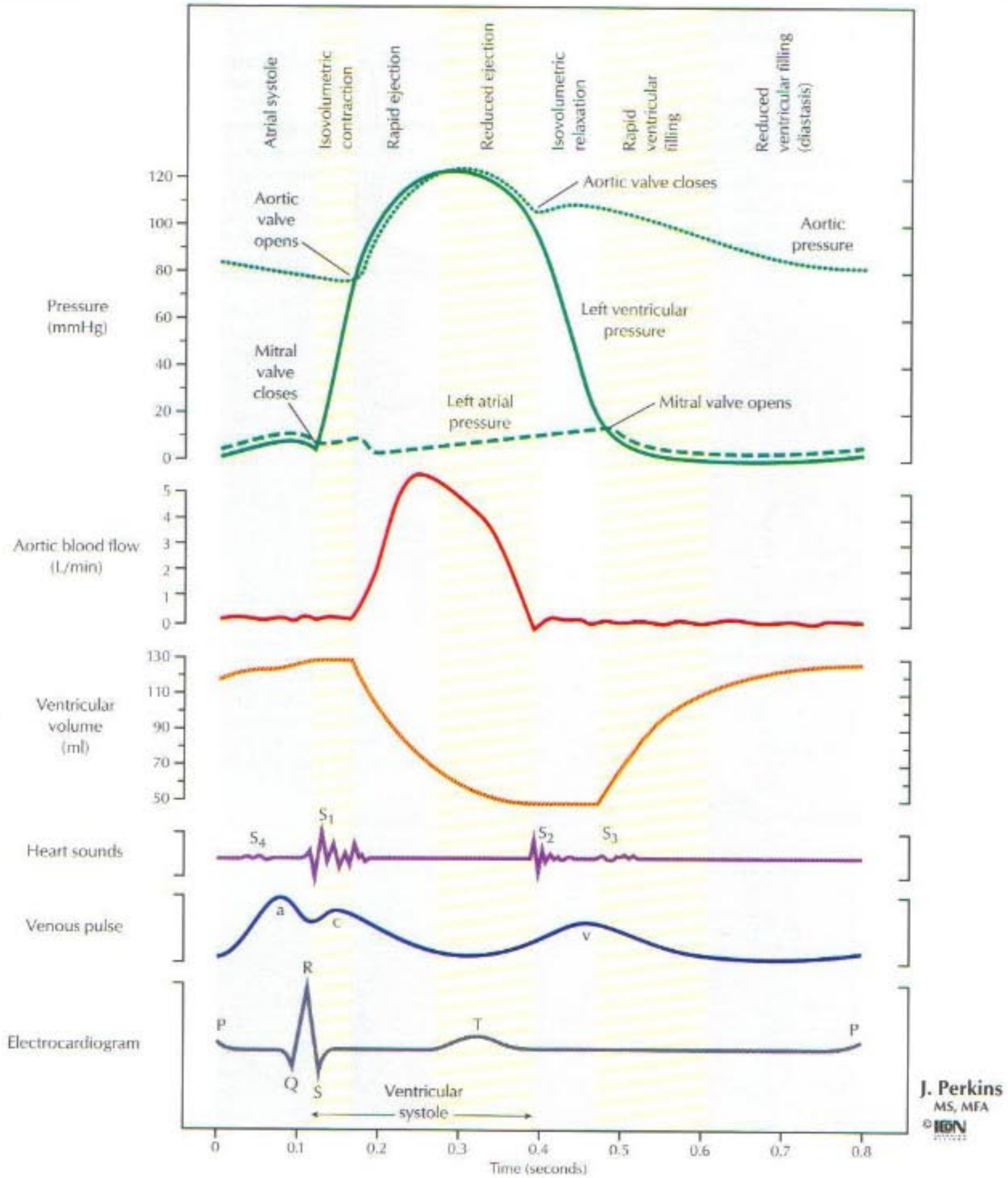


FIGURE 4.9 CARDIAC CYCLE

The cardiac cycle represents one complete sequence of atrial and ventricular contraction and relaxation. Depicted here are the key electrical and hemodynamic events associated with a single cycle. Changes in left atrial, ventricular, and aortic pressure; aortic blood flow; ventricular volume; heart sounds; jugular venous pressure; and the ECG are shown. The S_1 heart sound results from the closing of the mitral and tricuspid valves, whereas the S_2 heart sound results from the closing of the aortic and pulmonic valves. Both S_3 and S_4 are sounds associated with filling of the ventricles. They are normally difficult to hear in healthy adults. S_3 is heard in healthy children and in states of high cardiac output. S_4 is associated with ventricular filling during atrial contraction. The components of the jugular venous pulse are the *a* wave, caused by right atrial contraction; the *c* wave, which results from bulging of the tricuspid valve into right atrium during right ventricular contraction; and the *v* wave, resulting from increased right atrial volume (and pressure) as venous blood fills this chamber before the opening of the tricuspid valve. The components of the ECG are described in Figures 4.6 to 4.8.

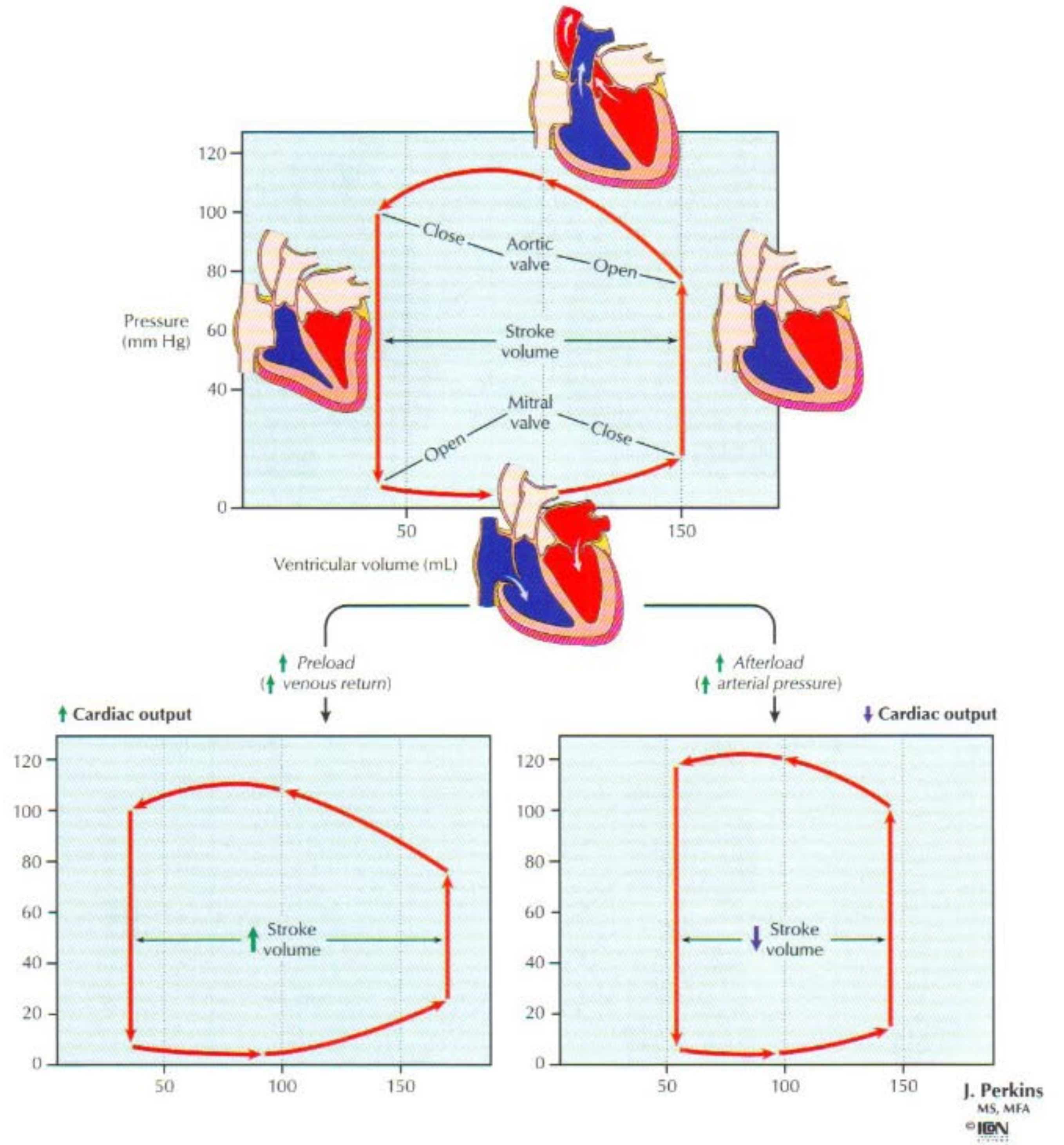

120
100
80
Pressure (mm Hg)
60
40
0
Close
Aortic valve
Open
Stroke volume
Mitral valve
Open
Close
50
150
Ventricular volume (mL)
↑ Preload
(↑ venous return)
↑ Afterload
(↑ arterial pressure)
↑ Cardiac output
↓ Cardiac output
120
100
80
60
40
20
0
↑ Stroke volume
50
100
150
120
100
80
60
40
20
0
↓ Stroke volume
50
100
150
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FIGURE 4.10 PRESSURE-VOLUME LOOP

Cardiac output is the volume of blood pumped by the heart each minute. In the steady state the output from both the right and left ventricles is the same. The pressure-volume loop for the left ventricle is depicted here. The cardiac output is calculated as:

Cardiac output = Heart rate × Stroke volume

where:

Stroke volume = End-diastolic volume − End-systolic volume

Increases in venous return (increased preload) increase the stroke volume and thus cardiac output. Increases in arterial pressure (increased afterload) decrease stroke volume and thus cardiac output (lower panel).

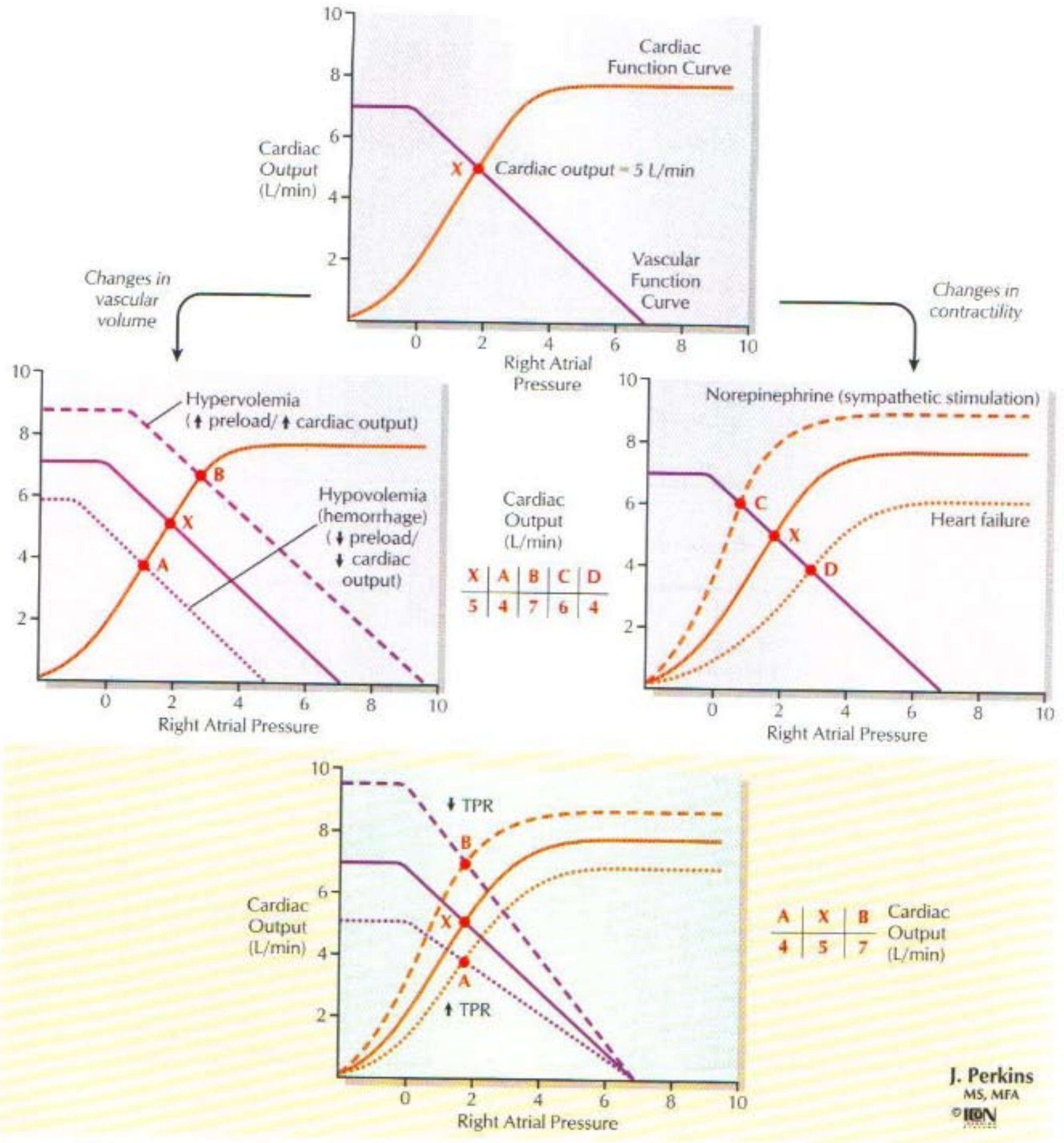

FIGURE 4.11 CARDIAC AND VASCULAR FUNCTION CURVES

The heart and blood vessels interact with each other to determine cardiac output. Depicted here are a series of vascular and cardiac function curves that illustrate this interaction. Changes in right atrial pressure affect venous return. Changes in vascular volume affect the vascular function curves, and changes in cardiac contractility affect the cardiac function curve. Changes in total peripheral resistance (TPR) affect both the vascular and cardiac function curves.

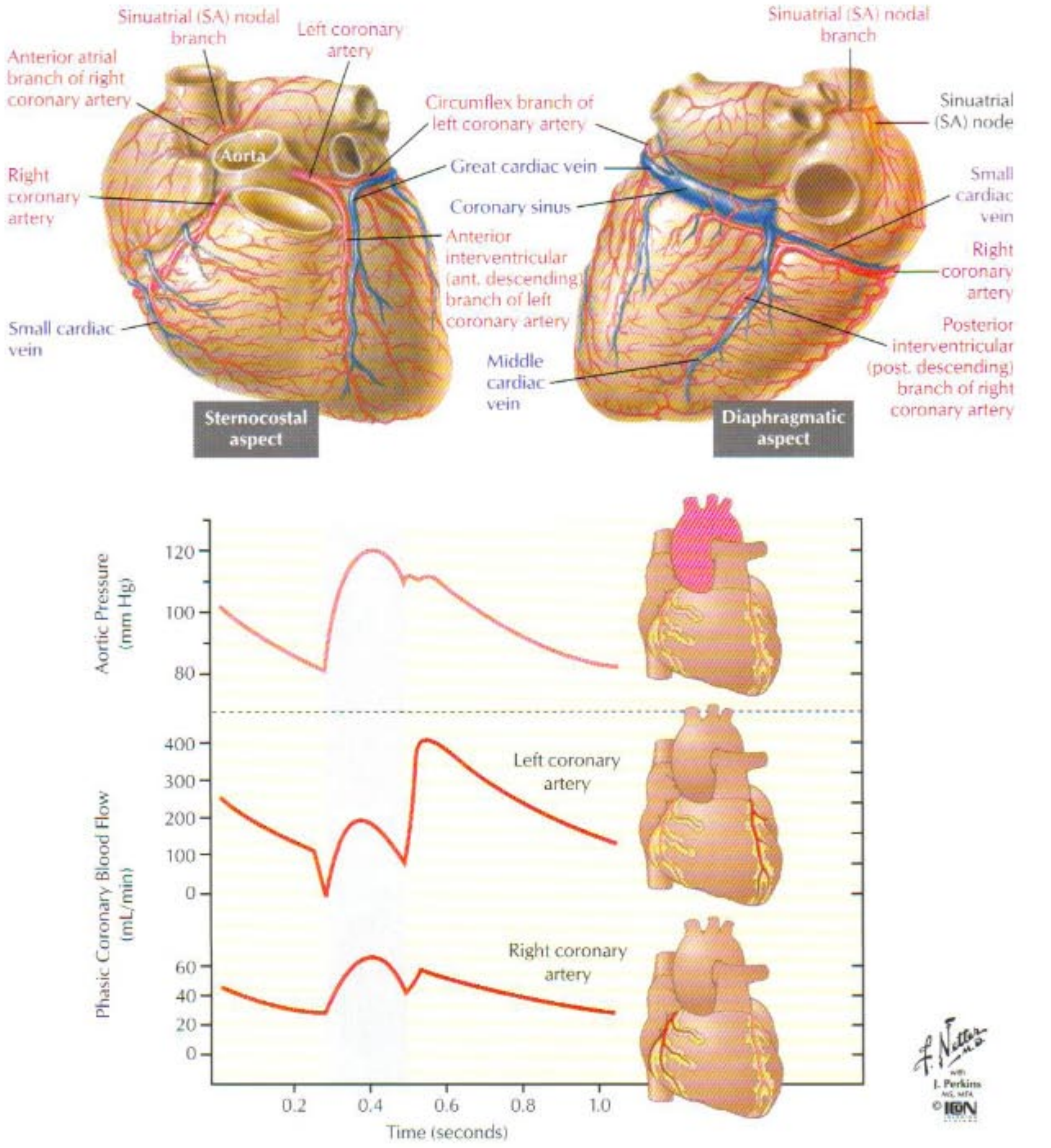
Sinuatrial (SA) nodal branch
Left coronary artery
Anterior atrial branch of right coronary artery
Aorta
Right coronary artery
Small cardiac vein
Circumflex branch of left coronary artery
Great cardiac vein
Coronary sinus
Anterior interventricular (ant. descending) branch of left coronary artery
Middle cardiac vein
Sternocostal aspect
Sinuatrial (SA) nodal branch
Sinuatrial (SA) node
Small cardiac vein
Right coronary artery
Posterior interventricular (post. descending) branch of right coronary artery
Diaphragmatic aspect
Aortic Pressure (mm Hg)
120
100
80
Phasic Coronary Blood Flow (mL/min)
400
300
200
100
0
Left coronary artery
60
40
20
0
Right coronary artery
0.2
0.4
0.6
0.8
1.0
Time (seconds)
F. Netter M.D.
with J. Perkins MS, MFA
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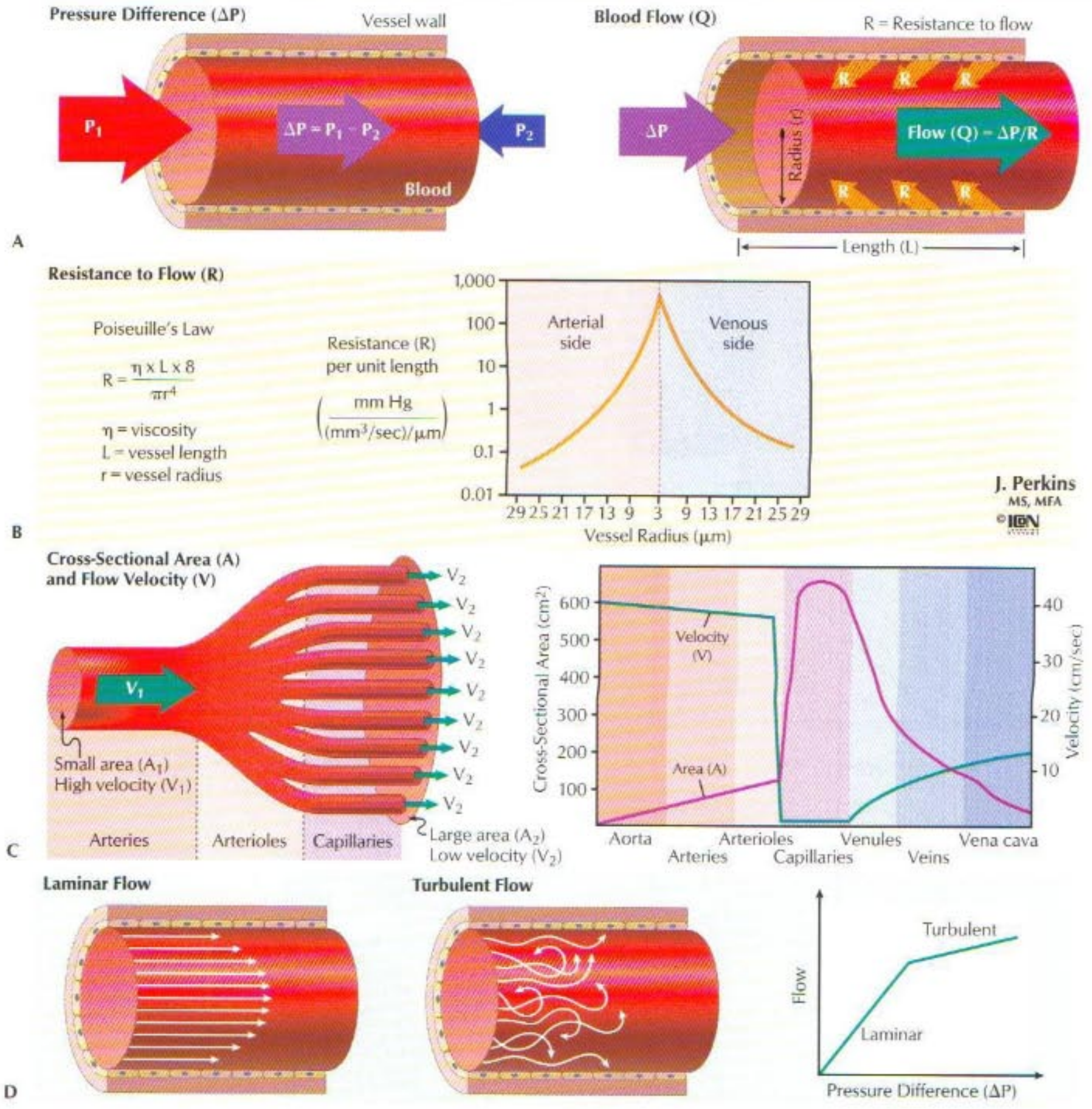
FIGURE 4.12 CORONARY CIRCULATION

The coronary arteries come off the aorta just above the aortic valve. Coronary blood flow varies with aortic pressure but is influenced by physical factors (compression of the vessels during contraction of the heart) and by metabolic factors released from the myocytes. Numerous metabolic factors have been implicated in the regulation of coronary blood flow (e.g., H^+, CO_2, decreased O_2, K^+, lactic acid, nitric oxide, adenosine). Of these factors, adenosine seems to be the most important. Thus, when cardiac work demand increases, adenosine released by the myocytes leads to vasodilation and thereby increased coronary blood flow.


Pressure Difference (ΔP)
Vessel wall
P1
ΔP = P1 − P2
P2
Blood
Blood Flow (Q)
R = Resistance to flow
ΔP
R
Radius (r)
Flow (Q) = ΔP/R
Length (L)
A
Resistance to Flow (R)
Poiseuille's Law
R = η x L x 8 / πr⁴
η = viscosity
L = vessel length
r = vessel radius
Resistance (R) per unit length
(mm Hg / (mm³/sec)/μm)
1,000
100
10
1
0.1
0.01
Arterial side
Venous side
29 25 21 17 13 9 3 9 13 17 21 25 29
Vessel Radius (μm)
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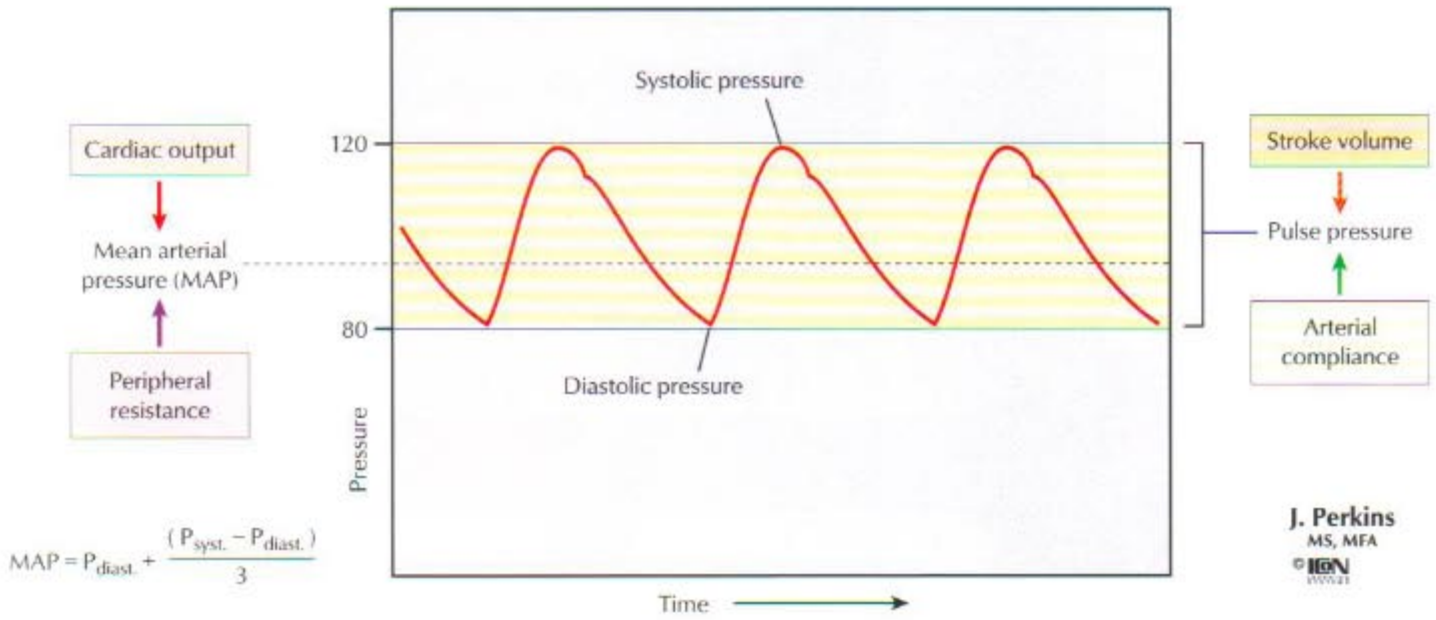
B
Cross-Sectional Area (A) and Flow Velocity (V)
V1
V2
Small area (A1) High velocity (V1)
Large area (A2) Low velocity (V2)
Arteries
Arterioles
Capillaries
Cross-Sectional Area (cm²)
600
500
400
300
200
100
Velocity (V)
Area (A)
40
30
20
10
Velocity (cm/sec)
Aorta
Arteries
Arterioles
Capillaries
Venules
Veins
Vena cava
C
Laminar Flow
Turbulent Flow
Turbulent
Laminar
Flow
Pressure Difference (ΔP)
D

FIGURE 4.13 HEMODYNAMICS

Panel A: The flow of blood flow through a vessel (Q) depends on the pressure difference (ΔP) and the resistance to flow (R). In the systemic circulation, ΔP = aortic pressure − right atrial pressure, and R = the total peripheral resistance (TPR). *Panel B:* As described by Poiseuille's law, the most important factor determining resistance to blood flow is the radius of the vessel. The small arterioles and capillaries have the highest resistance. Because of their ability to regulate their tone, the small arterioles are the most important vessels involved in regulating the TPR. *Panel C:* As blood flows from the aorta it courses through an increasingly branched arterial system. This branching increases the total cross-sectional area through which the blood flows and reduces the velocity of this flow (V = Q/A). The reduced flow velocity in the capillaries facilitates the exchange of fluids and nutrients across the capillary wall by allowing sufficient time for diffusion to occur. *Panel D:* Normally, blood flow through most of the vascular system is laminar. The exception is at the root of the aorta. However, in pathological conditions (e.g., lesions of the heart valves, narrowing or partial blockage of vessels), turbulent flow occurs and can be heard with the stethoscope as murmurs (in the heart) or bruits (in vessels). Laminar flow reduces the pressure gradient needed to propel the blood through the vessel.


Systolic pressure
Cardiac output
Mean arterial pressure (MAP)
Peripheral resistance
120
80
Diastolic pressure
Pressure
Time
Stroke volume
Pulse pressure
Arterial compliance

$$MAP = P_{diast.} + \frac{(P_{syst.} - P_{diast.})}{3}$$

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FIGURE 4.14 ARTERIAL PRESSURE

The mean arterial pressure (MAP) is the average pressure in the arteries averaged over time. It is determined by the cardiac output (CO) and the total peripheral resistance (TPR) as: MAP = CO × TPR. As described in Figure 4.10, CO is determined by the stroke volume (SV) and heart rate (HR) as: CO = SV × HR. Blood volume is an important determinant of SV. The sympathetic nervous system and a number of hormones (see Figure 4.15) determine vascular resistance. As a result of the heart's rhythmic pumping, the arterial pressure is pulsatile. The pulse pressure depends on the SV (large SV increases the pulse pressure) and the compliance of the arterial wall (decreased compliance increases pulse pressure). With normal aging, compliance of the arterial wall increases and results in an increase in the pulse pressure.

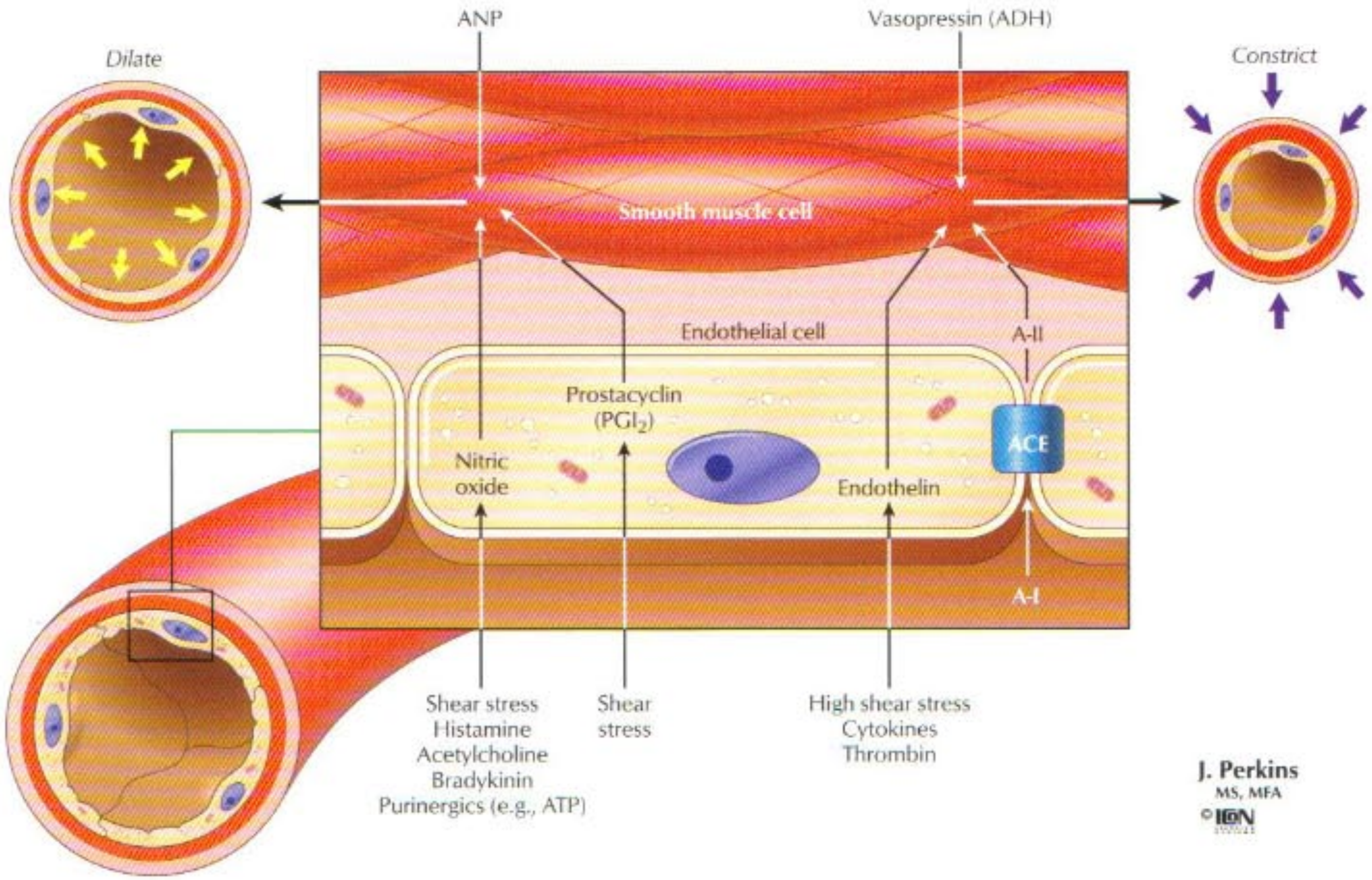
ANP
Vasopressin (ADH)
Dilate
Constrict
Smooth muscle cell
Endothelial cell
A-II
Prostacyclin
(PGI$_2$)
Nitric
oxide
ACE
Endothelin
A-I
Shear stress
Histamine
Acetylcholine
Bradykinin
Purinergics (e.g., ATP)
Shear
stress
High shear stress
Cytokines
Thrombin
J. Perkins
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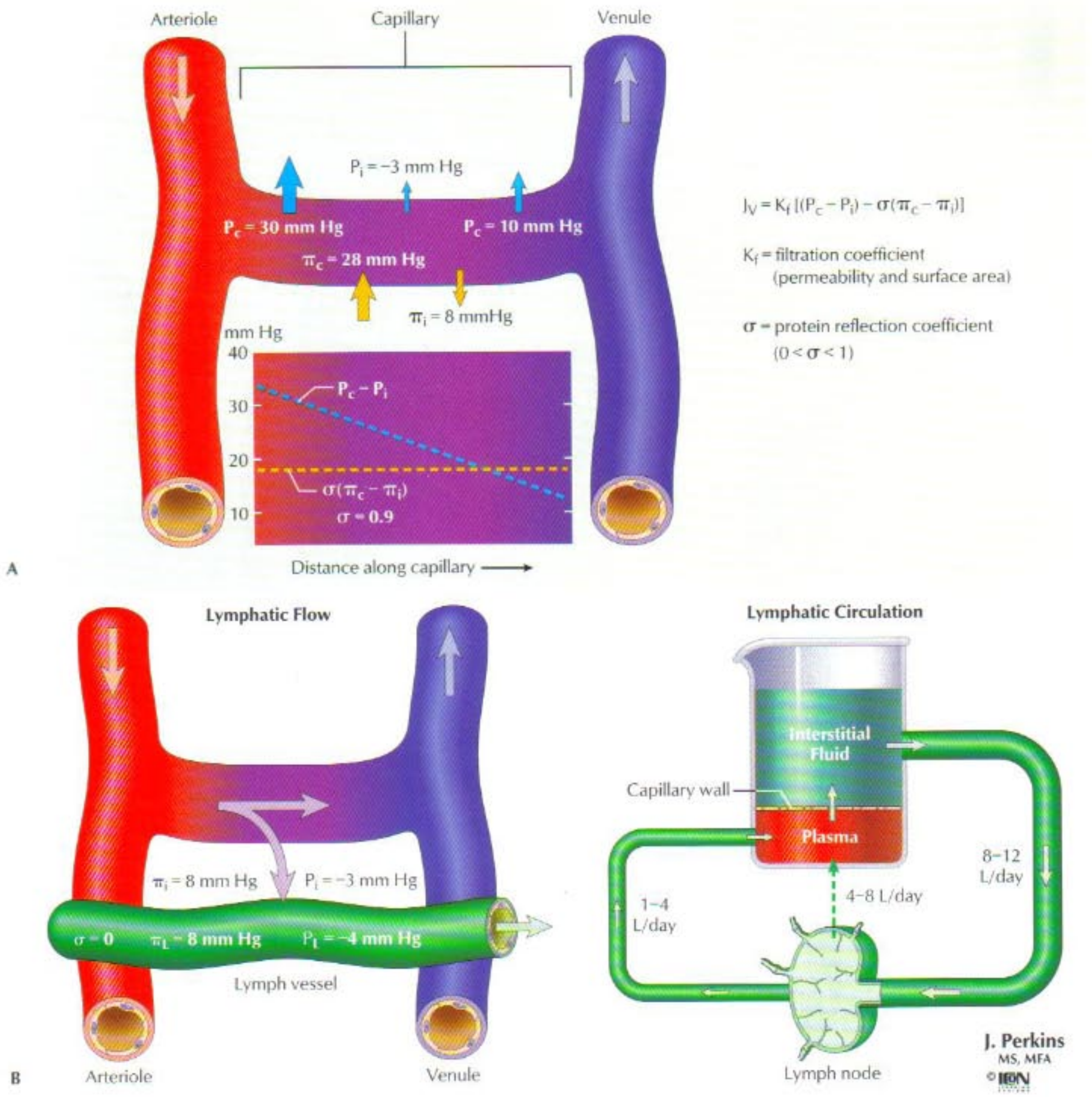
FIGURE 4.15 CONTROL OF ARTERIOLAR TONE

Small arterioles are the major determinants of the resistance of the vascular system. Release of norepinephrine by sympathetic nerves contributes to the resting tone of the smooth muscle cell and, with increased sympathetic firing, further increases tone. Circulating hormones such as atrial natriuretic peptide (ANP), angiotensin II (A-II) and vasopressin (ADH) also act on the arterial smooth muscle cells to alter their tone. Substances produced by the endothelial cells in response to a host of factors (e.g., shear stress due to blood flowing through the vessel and acetylcholine released from parasympathetic nerves) act on the adjacent arterial smooth muscle cells to modulate their tone. The surface of the endothelial cell also contains angiotensin-converting enzyme (ACE), which is necessary to convert the inactive angiotensin I (A-I) molecule to its active form, A-II.


Arteriole
Capillary
Venule
P_i = −3 mm Hg
P_c = 30 mm Hg
P_c = 10 mm Hg
π_c = 28 mm Hg
π_i = 8 mmHg
mm Hg
40
30
20
10
P_c − P_i
σ(π_c − π_i)
σ = 0.9
Distance along capillary
A
Lymphatic Flow
π_i = 8 mm Hg
P_i = −3 mm Hg
σ = 0
π_L = 8 mm Hg
P_L = −4 mm Hg
Lymph vessel
B
Arteriole
Venule
Lymphatic Circulation
Interstitial Fluid
Capillary wall
Plasma
8–12 L/day
4–8 L/day
1–4 L/day
Lymph node
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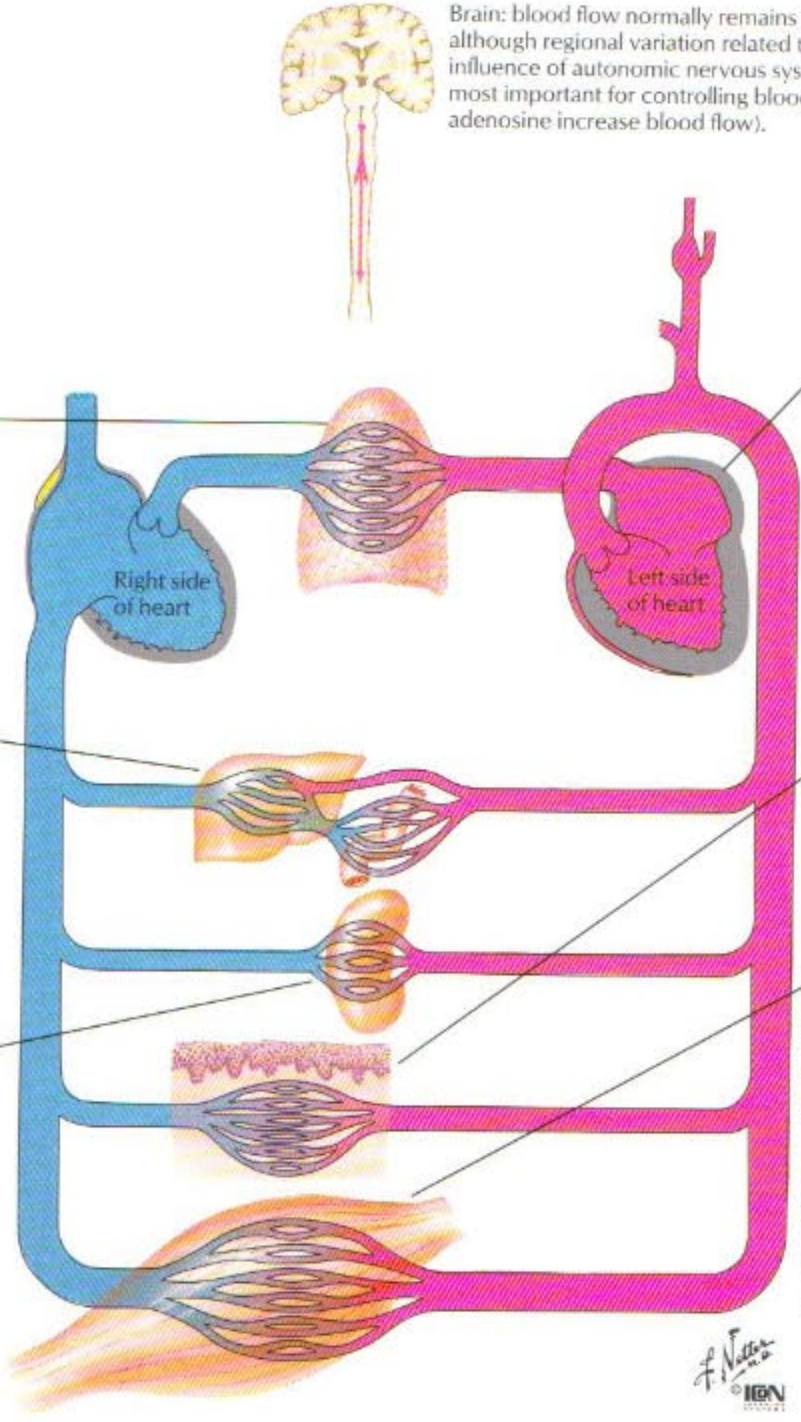
$J_V = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$

K_f = filtration coefficient (permeability and surface area)

σ = protein reflection coefficient ($0 < \sigma < 1$)

FIGURE 4.16 MICROCIRCULATION

Exchange of O_2, CO_2, nutrients, cellular metabolites, and fluid occurs across the capillary wall by both diffusion and bulk flow. As shown in *panel A*, bulk flow of fluid across the capillary wall is driven by the Starling forces (i.e., hydrostatic pressure − P and oncotic pressure generated by proteins − Π). Hydrostatic pressure results from the pumping of blood by the heart, as well as the effect of gravity on the column of blood in a vessel. Oncotic pressure represents the osmotic pressure generated by proteins. In addition to these Starling forces, the volume of fluid moving across the capillary wall depends on the filtration coefficient (K_f), which reflects the intrinsic permeability of the wall and its surface area. The proteins in plasma and interstitial fluid can exert an osmotic pressure only if they do not readily cross the capillary wall. The ease with which proteins cross the wall is expressed by the reflection coefficient (σ). Proteins do not easily cross the wall in skeletal muscle capillaries ($\sigma = 0.9$) and therefore play an important role in fluid movement. However, liver capillaries (termed sinusoids) are highly permeable to proteins. As a result, $\sigma = 0$, and the protein oncotic pressure does not contribute to the movement of fluid across the sinusoid wall (i.e., fluid movement in the liver sinusoid occurs only by hydrostatic pressure). *Panel B:* In most capillary beds there is net movement of fluid out of the capillary into the interstitium. This fluid is carried away by lymphatic vessels and returned to the vascular compartment either at lymph nodes or by the thoracic and right lymphatic ducts.



Brain: blood flow normally remains constant (autoregulation), although regional variation related to brain activity occurs. Little influence of autonomic nervous system. Local metabolic factors most important for controlling blood flow (e.g. H+, CO_2, O_2, and adenosine increase blood flow).

Lungs: important to match perfusion to ventilation. Little influence of autonomic nervous system. Changes in O_2 tension most important in regulating blood flow (decreased O_2 decreases blood flow, and increased O_2 increases blood flow)

Coronary arteries: flow interrupted during systole. Little influence of autonomic nervous system. Local metabolic factors most important for controlling blood flow (e.g., adenosine, NO, and decreased O_2 increase blood flow)

Liver and splanchnic beds: blood flow regulated to facilitate digestion. Sympathetic nerves decrease blood flow, and parasympathetic nerves increase blood flow. GI hormones (gastrin, cholecystokinin, secretin) increase blood flow, as do products of digestion (glucose and fatty acids)

Skin: blood flow altered for thermoregulation. Sympathetic nerves decrease blood flow (α-receptors). Circulating hormones also affect blood flow. A-II and vasopressin decrease blood flow; ANP increases blood flow

Kidneys: blood flow normally maintained constant (autoregulation) to maintain normal glomerular filtration. Sympathetic nerves decrease blood flow. Circulating hormones also affect blood flow (A-II and vasopressin decrease blood flow; ANP increases blood flow)

Skeletal muscle: major determinant of total peripheral resistance. Blood flow regulated in response to exercise. Basal flow set by sympathetic nerves. Circulating hormones also affect flow (A-II and vasopressin decrease blood flow; ANP increases blood flow). With exercise, release of metabolites (e.g. H+, lactate, CO_2, O_2, adenosine) increases blood flow

FIGURE 4.17 CIRCULATION TO SPECIAL REGIONS

Blood flow to different vascular beds is regulated by a number of factors and in response to the physiological demands of the tissues.

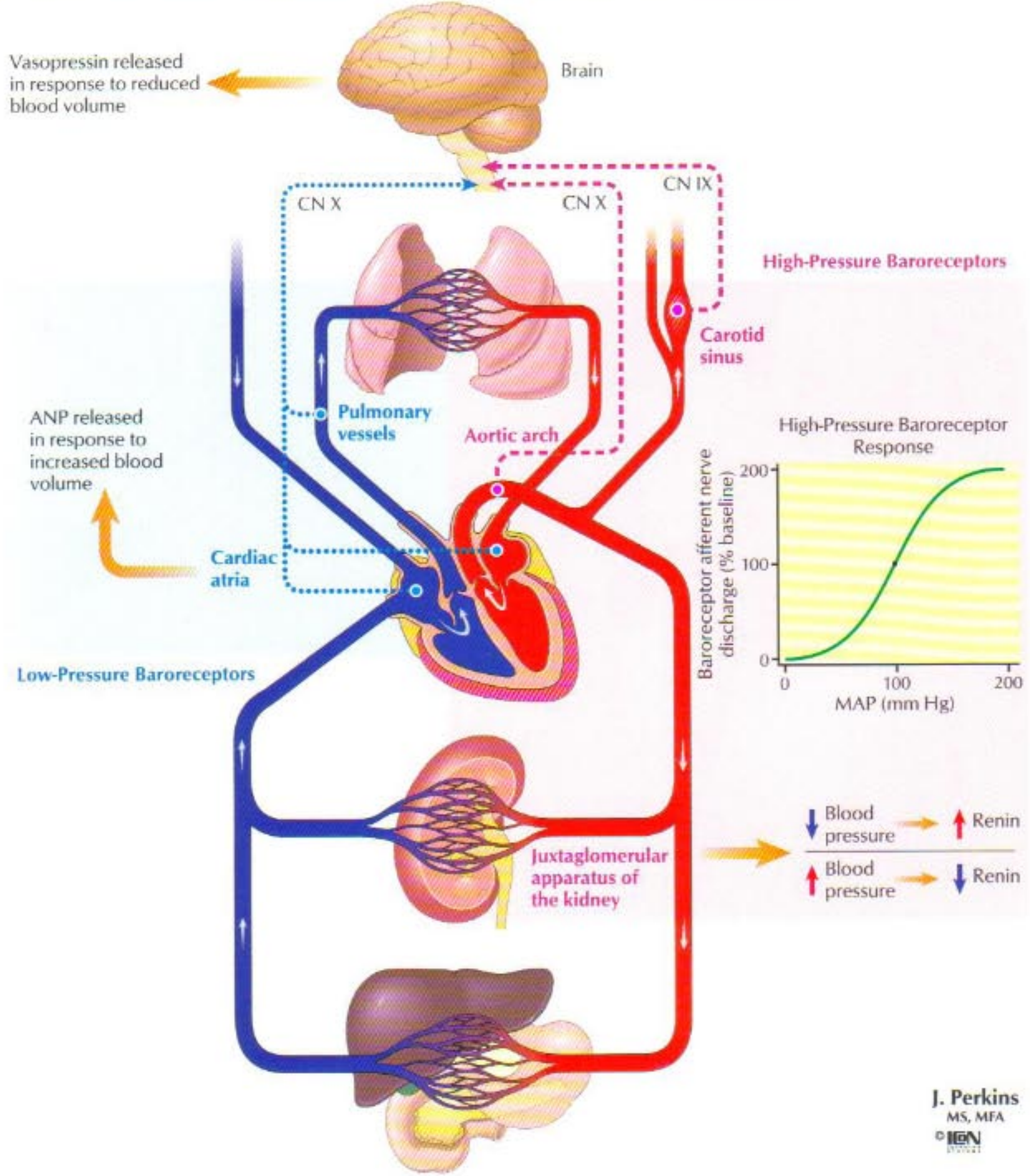

Vasopressin released in response to reduced blood volume
Brain
CN IX
CN X
CN X
High-Pressure Baroreceptors
Carotid sinus
Pulmonary vessels
Aortic arch
ANP released in response to increased blood volume
Cardiac atria
Low-Pressure Baroreceptors
High-Pressure Baroreceptor Response
Baroreceptor afferent nerve discharge (% baseline)
200
100
0
0
100
200
MAP (mm Hg)
Juxtaglomerular apparatus of the kidney
Blood pressure
Renin
Blood pressure
Renin
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FIGURE 4.18 MONITORING OF BLOOD PRESSURE

The body has a complex system to monitor and regulate blood pressure (BP). This system is critically important for the maintenance of BP during all aspects of daily life (e.g., rising from a sitting to a standing position or during exercise), as well as during abnormal conditions (e.g., excessive fluid loss in a hot environment or hemorrhage). Pressure sensors (termed baroreceptors) are located in the high-pressure (arterial) and low-pressure (venous) sides of the circulatory system. High-pressure baroreceptors in the aortic arch and carotid sinus monitor arterial BP and send signals to the brainstem in the vagus (CN X) and glossopharyngeal (CN IX) nerves. These signals result in alterations in sympathetic nerve activity (not shown). The afferent arterioles of the juxtaglomerular apparatus are also high-pressure baroreceptors. They respond to changes in arterial BP by varying the secretion of the proteolytic enzyme renin. As described in Figure 6.12, renin results in the production of angiotensin II, a potent vasoconstrictor (see Figure 4.15). Low-pressure baroreceptors are found in the large pulmonary vessels and the atria of the heart. By their location, they respond primarily to changes in blood volume. These baroreceptors send signals to the brain in the vagus nerve (CN X), which, in addition to altering sympathetic nerve activity, cause the release of vasopressin (ADH). When stretched (i.e., increased blood volume), the atria also secrete the hormone atrial natriuretic peptide (ANP), which increases the excretion of NaCl and water by the kidneys (see Figure 4.20) and decreases arterial tone (see Figure 4.15).

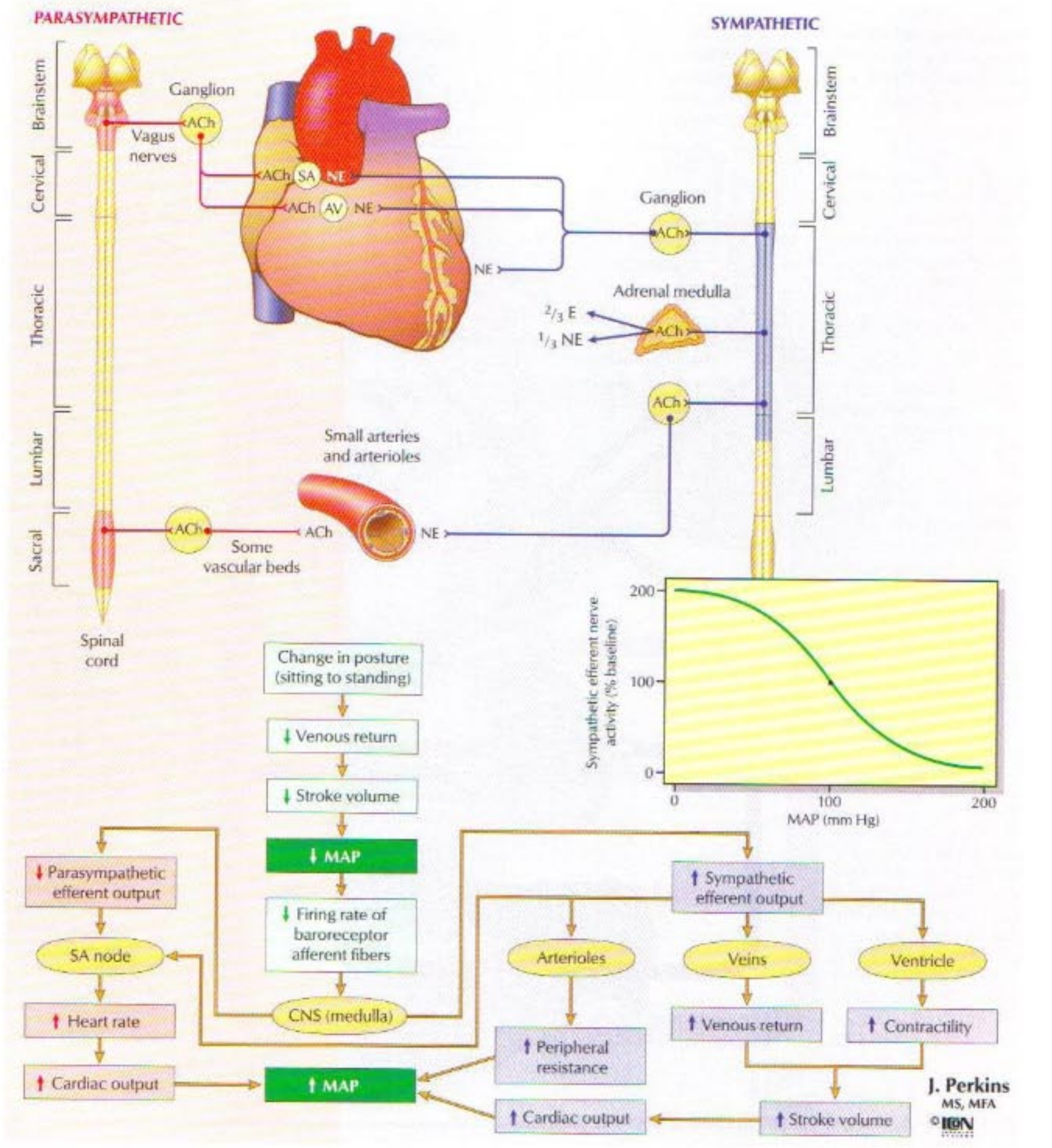
PARASYMPATHETIC
SYMPATHETIC
Brainstem
Cervical
Thoracic
Lumbar
Sacral
Ganglion
ACh
Vagus nerves
ACh SA NE
ACh AV NE
NE
Ganglion
ACh
Adrenal medulla
2/3 E
1/3 NE
ACh
ACh
Small arteries and arterioles
ACh
ACh
Some vascular beds
NE
Spinal cord
Brainstem
Cervical
Thoracic
Lumbar
Sympathetic efferent nerve activity (% baseline)
200
100
0
0
100
200
MAP (mm Hg)
Change in posture (sitting to standing)
↓ Venous return
↓ Stroke volume
↓ MAP
↓ Firing rate of baroreceptor afferent fibers
CNS (medulla)
↓ Parasympathetic efferent output
SA node
↑ Heart rate
↑ Cardiac output
↑ MAP
↑ Sympathetic efferent output
Arterioles
Veins
Ventricle
↑ Peripheral resistance
↑ Venous return
↑ Contractility
↑ Stroke volume
↑ Cardiac output
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FIGURE 4.19 SHORT-TERM RESPONSE TO CHANGES IN BLOOD PRESSURE

The autonomic nervous system is primarily involved in maintaining blood pressure on a second-by-second basis. This is illustrated for a change in posture. *ACh*, Acetylcholine; *E*, epinephrine; *NE*, norepinephrine; *MAP*, mean arterial pressure.

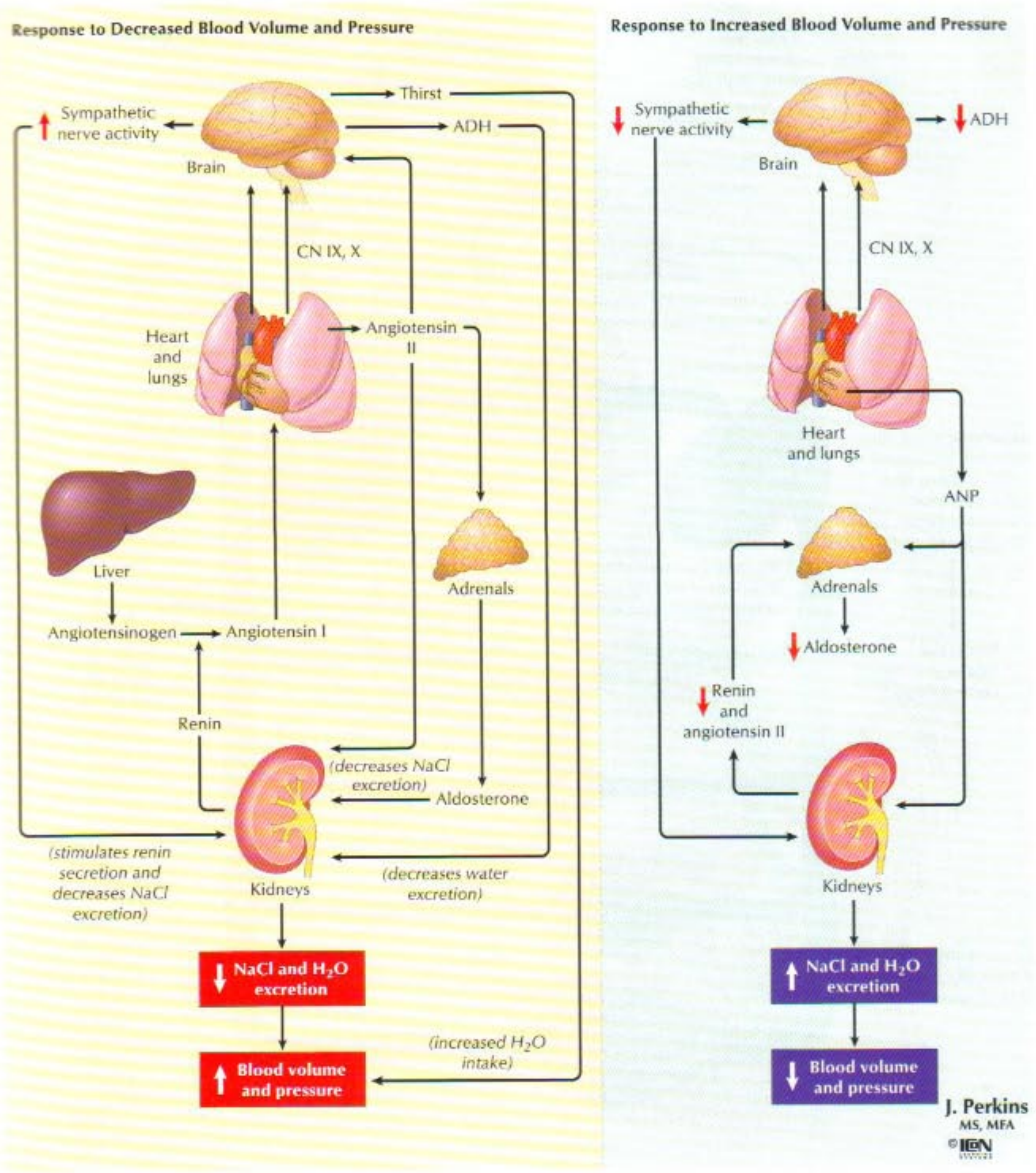
Response to Decreased Blood Volume and Pressure
↑ Sympathetic nerve activity
Thirst
ADH
Brain
CN IX, X
Heart and lungs
Angiotensin II
Liver
Adrenals
Angiotensinogen
Angiotensin I
Renin
(decreases NaCl excretion)
Aldosterone
(stimulates renin secretion and decreases NaCl excretion)
Kidneys
(decreases water excretion)
↓ NaCl and H₂O excretion
(increased H₂O intake)
↑ Blood volume and pressure
Response to Increased Blood Volume and Pressure
↓ Sympathetic nerve activity
↓ ADH
Brain
CN IX, X
Heart and lungs
ANP
Adrenals
↓ Aldosterone
↓ Renin and angiotensin II
Kidneys
↑ NaCl and H₂O excretion
↓ Blood volume and pressure
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FIGURE 4.20 LONG-TERM RESPONSE TO CHANGES IN BLOOD VOLUME AND PRESSURE

When blood volume (and pressure) changes, the kidneys respond by either retaining NaCl and water or excreting NaCl and water in order to restore blood volume to its normal value. With increased sympathetic nerve activity, norepinephrine and epinephrine secretion by the adrenal medulla will be stimulated (not shown). These circulating catecholamines will also act on the kidney to reduce NaCl excretion.

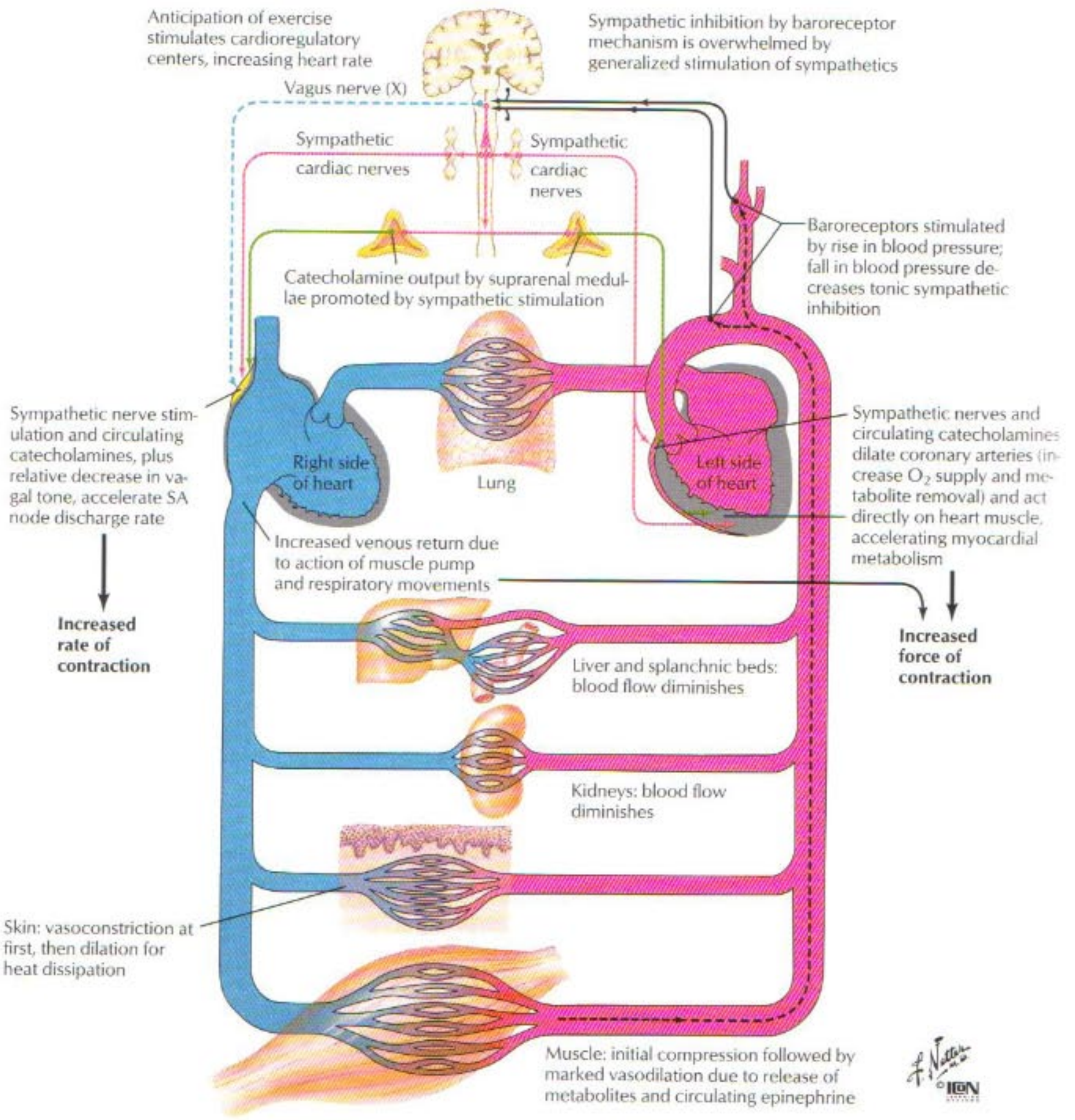
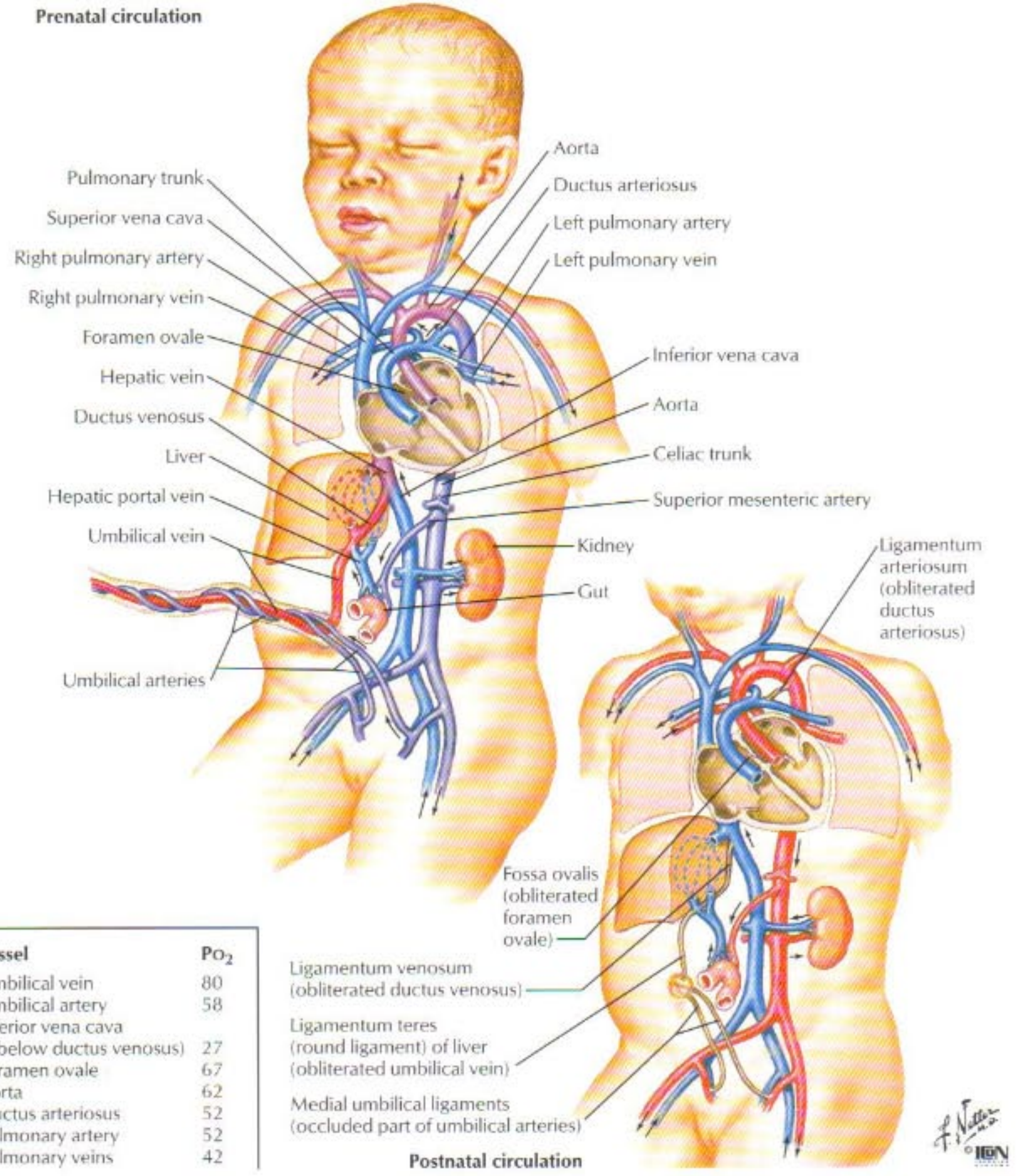

Anticipation of exercise stimulates cardioregulatory centers, increasing heart rate
Sympathetic inhibition by baroreceptor mechanism is overwhelmed by generalized stimulation of sympathetics
Vagus nerve (X)
Sympathetic cardiac nerves
Sympathetic cardiac nerves
Baroreceptors stimulated by rise in blood pressure; fall in blood pressure decreases tonic sympathetic inhibition
Catecholamine output by suprarenal medullae promoted by sympathetic stimulation
Sympathetic nerve stimulation and circulating catecholamines, plus relative decrease in vagal tone, accelerate SA node discharge rate
Right side of heart
Lung
Left side of heart
Sympathetic nerves and circulating catecholamines dilate coronary arteries (increase O_2 supply and metabolite removal) and act directly on heart muscle, accelerating myocardial metabolism
Increased venous return due to action of muscle pump and respiratory movements
Increased rate of contraction
Increased force of contraction
Liver and splanchnic beds: blood flow diminishes
Kidneys: blood flow diminishes
Skin: vasoconstriction at first, then dilation for heat dissipation
Muscle: initial compression followed by marked vasodilation due to release of metabolites and circulating epinephrine

FIGURE 4.21 CIRCULATORY RESPONSE TO EXERCISE

This figure summarizes the integrated neural and chemical effects of exercise on the cardiovascular system. Neural effects are mediated centrally (by the autonomic nervous system), whereas the chemical effects are mediated locally by the release of vasoactive metabolites and the effects of circulating catecholamines (e.g., epinephrine).


Prenatal circulation
Pulmonary trunk
Superior vena cava
Right pulmonary artery
Right pulmonary vein
Foramen ovale
Hepatic vein
Ductus venosus
Liver
Hepatic portal vein
Umbilical vein
Umbilical arteries
Aorta
Ductus arteriosus
Left pulmonary artery
Left pulmonary vein
Inferior vena cava
Aorta
Celiac trunk
Superior mesenteric artery
Kidney
Gut
Ligamentum arteriosum (obliterated ductus arteriosus)
Fossa ovalis (obliterated foramen ovale)
Ligamentum venosum (obliterated ductus venosus)
Ligamentum teres (round ligament) of liver (obliterated umbilical vein)
Medial umbilical ligaments (occluded part of umbilical arteries)
Postnatal circulation

Vessel	Po_2
Umbilical vein	80
Umbilical artery	58
Inferior vena cava (below ductus venosus)	27
Foramen ovale	67
Aorta	62
Ductus arteriosus	52
Pulmonary artery	52
Pulmonary veins	42

FIGURE 4.22 PRENATAL AND POSTNATAL CIRCULATION

This figure summarizes prenatal and postnatal circulation. Postnatally, blood no longer passes through the placenta but does perfuse the lungs. Consequently, prenatal shunts that delivered blood to the placenta and back to the fetus (umbilical arteries and umbilical vein) become ligaments. Likewise, shunts bypassing the liver (ductus venosus), the right ventricle (foramen ovale), and the pulmonary circulation (ductus arteriosus) also close, providing for the pulmonary and systemic circulations that characterize the normal postnatal pattern. Values on the lower left represent relative percentages of O_2 saturation of the blood at various points along the fetal circulation.

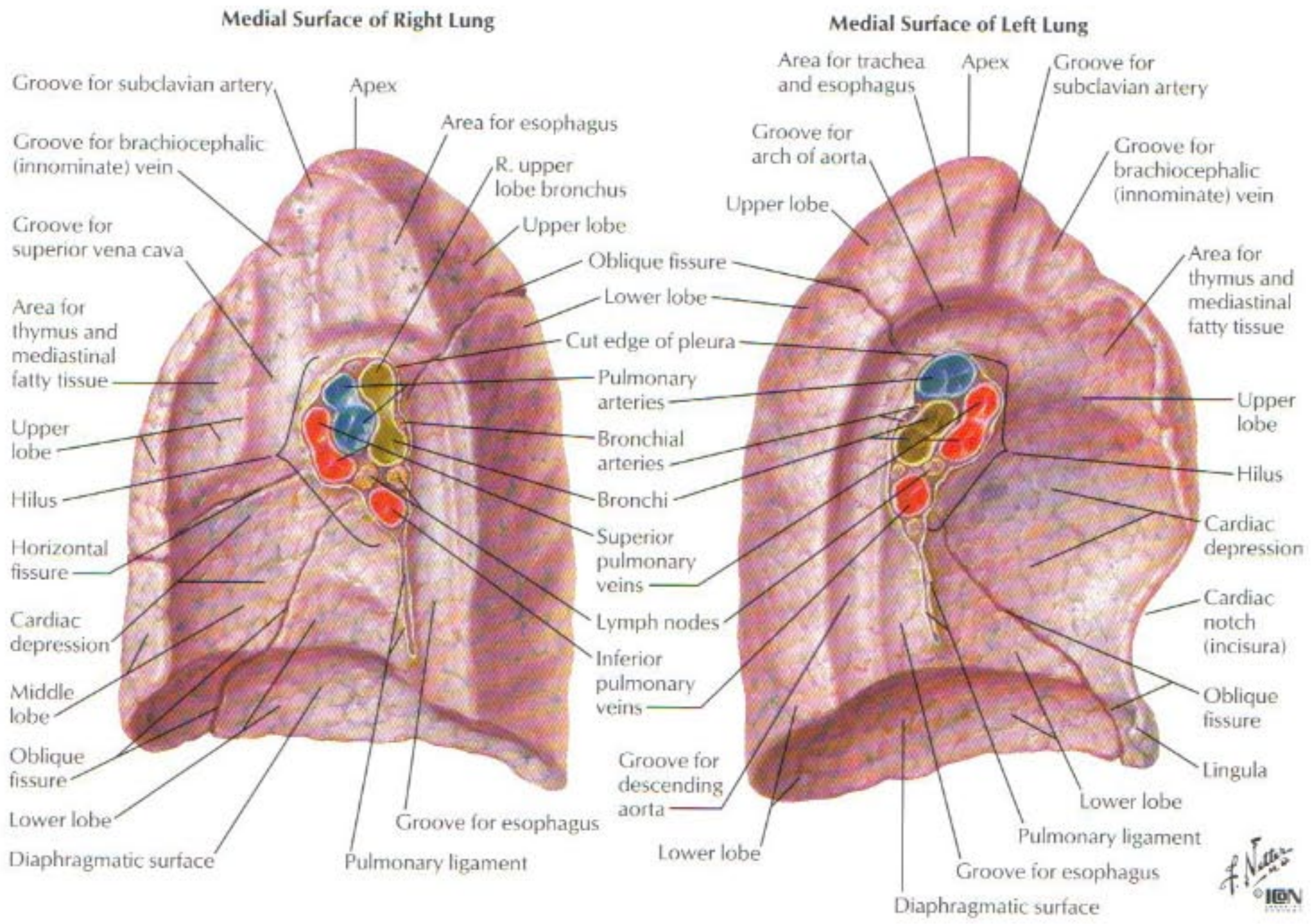

Medial Surface of Right Lung
Groove for subclavian artery
Apex
Area for esophagus
R. upper lobe bronchus
Groove for brachiocephalic (innominate) vein
Upper lobe
Groove for superior vena cava
Oblique fissure
Lower lobe
Area for thymus and mediastinal fatty tissue
Cut edge of pleura
Pulmonary arteries
Upper lobe
Bronchial arteries
Hilus
Bronchi
Superior pulmonary veins
Horizontal fissure
Lymph nodes
Cardiac depression
Inferior pulmonary veins
Middle lobe
Oblique fissure
Lower lobe
Groove for esophagus
Diaphragmatic surface
Pulmonary ligament
Medial Surface of Left Lung
Area for trachea and esophagus
Apex
Groove for subclavian artery
Groove for arch of aorta
Groove for brachiocephalic (innominate) vein
Upper lobe
Area for thymus and mediastinal fatty tissue
Upper lobe
Hilus
Cardiac depression
Cardiac notch (incisura)
Oblique fissure
Lingula
Groove for descending aorta
Lower lobe
Pulmonary ligament
Lower lobe
Groove for esophagus
Diaphragmatic surface

FIGURE 5.1 MEDIAL SURFACE OF THE LUNGS

Breathing, or ventilation of the lungs, is an automatic, usually rhythmic, and centrally controlled process. The right lung has three lobes, and the left lung has two lobes, with the bronchi, pulmonary vessels, nerves, and lymphatics entering or leaving each lung at the hilum, which is situated on the medial aspect of the lung. The trachea bifurcates into primary bronchi, which then enter the lobes of the lung and further subdivide into smaller and smaller segments (bronchioles and ultimately alveolar ducts and sacs).

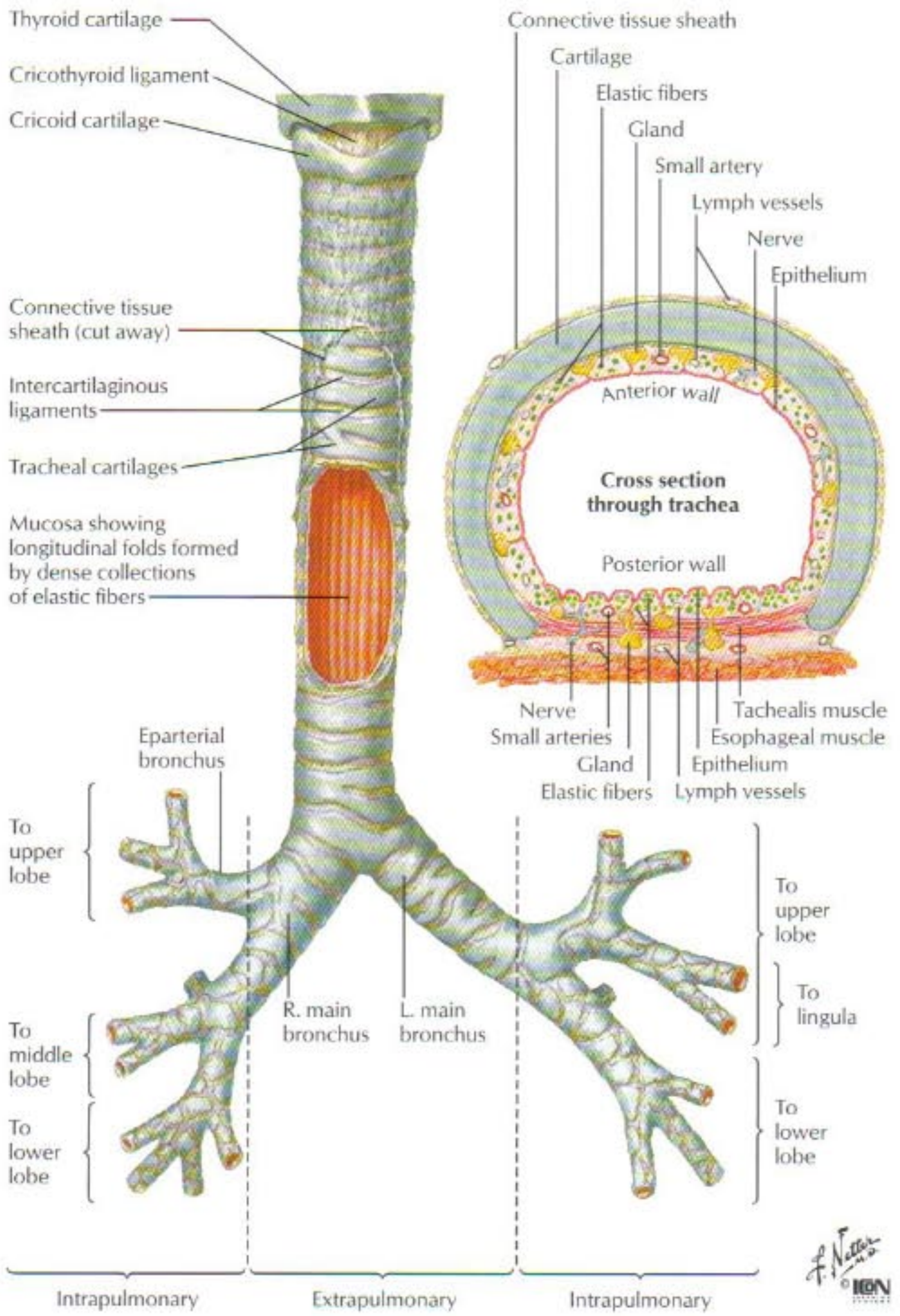

Thyroid cartilage
Cricothyroid ligament
Cricoid cartilage
Connective tissue sheath (cut away)
Intercartilaginous ligaments
Tracheal cartilages
Mucosa showing longitudinal folds formed by dense collections of elastic fibers
Eparterial bronchus
To upper lobe
To middle lobe
To lower lobe
R. main bronchus
L. main bronchus
To upper lobe
To lingula
To lower lobe
Intrapulmonary
Extrapulmonary
Intrapulmonary
Connective tissue sheath
Cartilage
Elastic fibers
Gland
Small artery
Lymph vessels
Nerve
Epithelium
Anterior wall
Cross section through trachea
Posterior wall
Nerve
Small arteries
Gland
Elastic fibers
Tachealis muscle
Esophageal muscle
Epithelium
Lymph vessels

FIGURE 5.2 STRUCTURE OF THE TRACHEA AND MAJOR BRONCHI

The major conducting airways to the lungs include the cartilaginous trachea, the right and left main bronchus, and the intrapulmonary bronchi passing through the lung parenchyma. With each subsequent branching, the conducting airways become smaller and smaller in diameter (see Figure 5.3), eventually losing their cartilaginous plates.

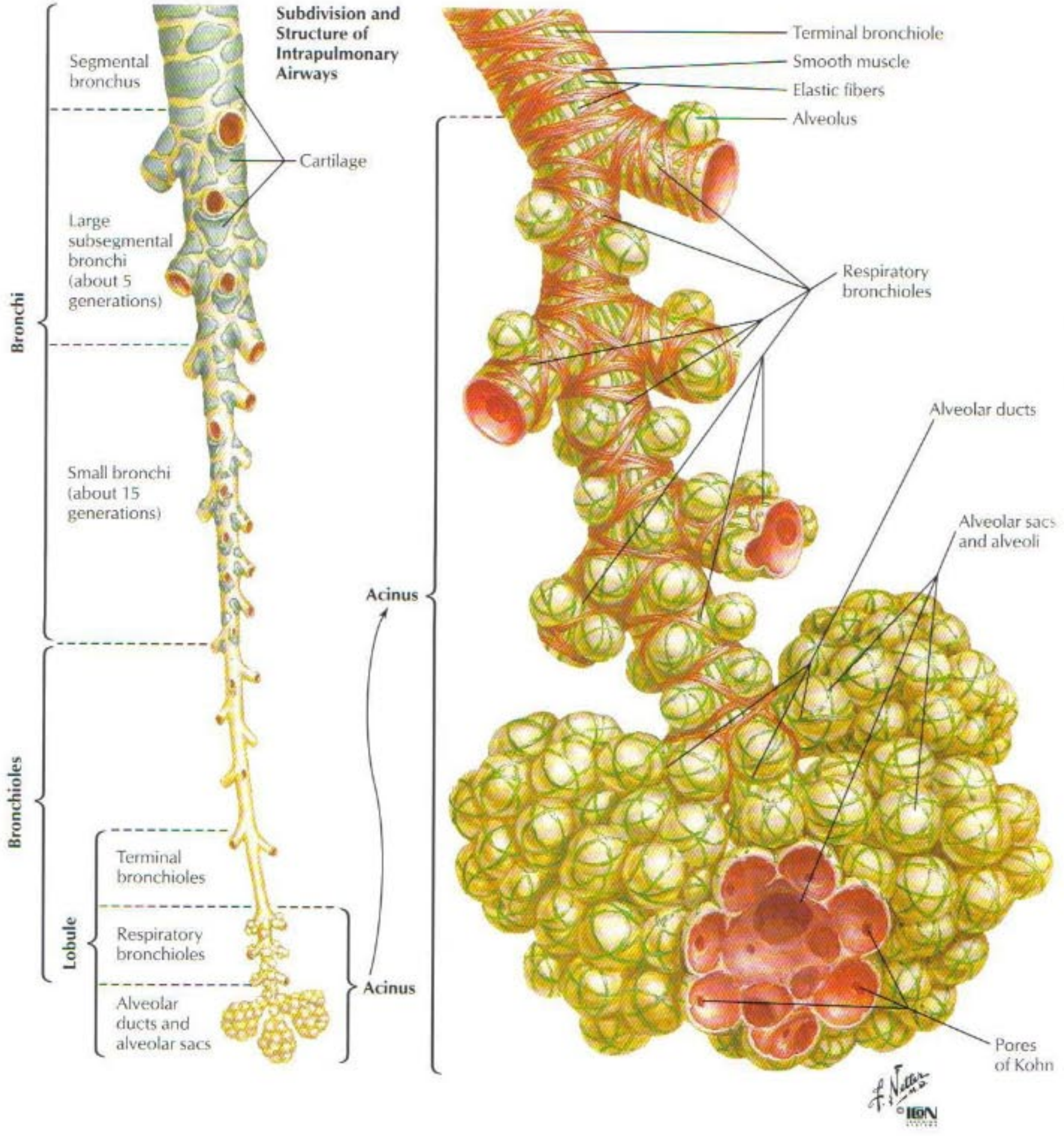
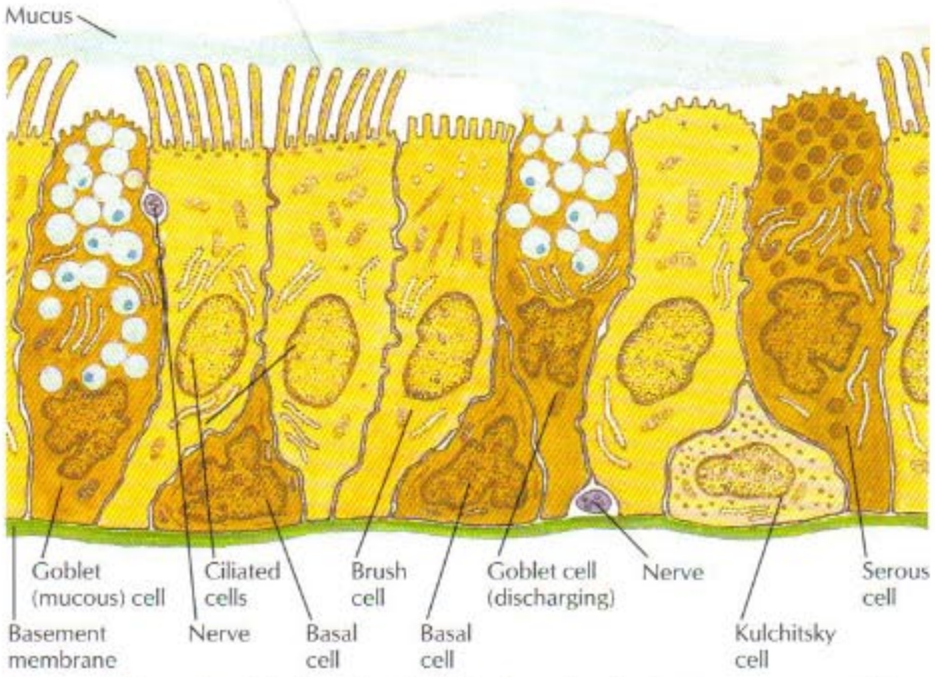
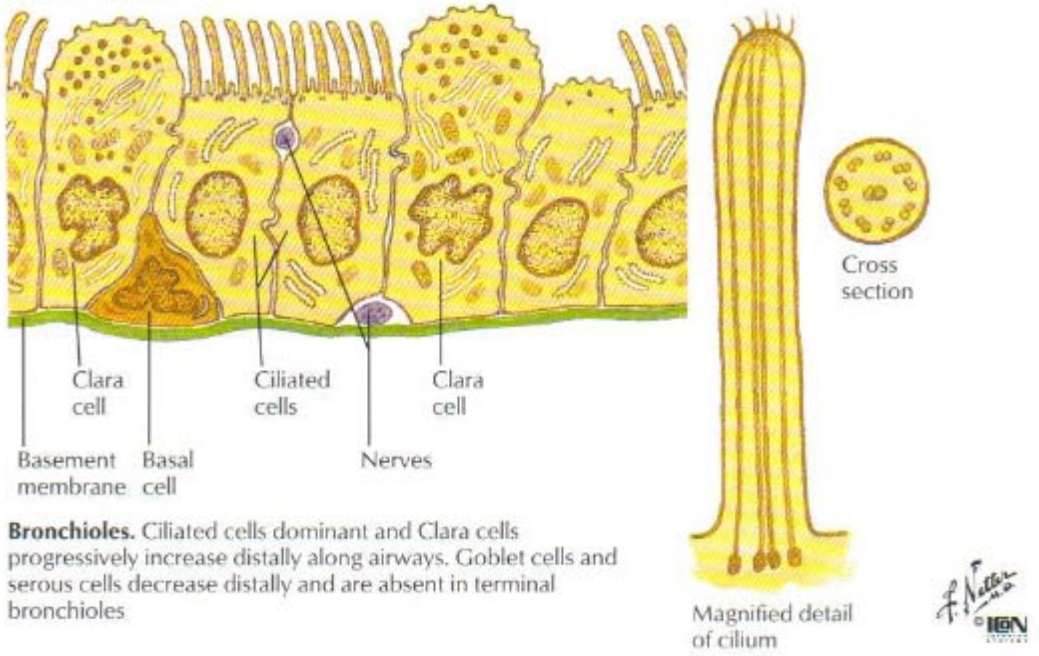

Subdivision and Structure of Intrapulmonary Airways
Segmental bronchus
Cartilage
Large subsegmental bronchi (about 5 generations)
Bronchi
Small bronchi (about 15 generations)
Bronchioles
Terminal bronchioles
Lobule
Respiratory bronchioles
Alveolar ducts and alveolar sacs
Acinus
Acinus
Terminal bronchiole
Smooth muscle
Elastic fibers
Alveolus
Respiratory bronchioles
Alveolar ducts
Alveolar sacs and alveoli
Pores of Kohn

FIGURE 5.3 INTRAPULMONARY AIRWAYS

As air enters the trachea during inspiration, it will pass through as few as 10 or as many as 23 generations, or branchings, on its journey to alveoli. The initial bronchi constitute the conducting zone and are incapable of gas exchange. Bronchioles represent a transitional zone with some alveoli, and the terminal bronchioles are lined with alveolar ducts and sacs, representing the respiratory zone.


Mucus
Goblet (mucous) cell
Ciliated cells
Brush cell
Goblet cell (discharging)
Nerve
Serous cell
Basement membrane
Nerve
Basal cell
Basal cell
Kulchitsky cell

Trachea and large bronchi. Ciliated and goblet cells predominant, with some serous cells and occasional brush cells and Clara cells. Numerous basal cells and occasional Kulchitsky cells are present


Clara cell
Ciliated cells
Clara cell
Basement membrane
Basal cell
Nerves
Cross section
Magnified detail of cilium
F. Netter M.D.
© ICON

Bronchioles. Ciliated cells dominant and Clara cells progressively increase distally along airways. Goblet cells and serous cells decrease distally and are absent in terminal bronchioles

FIGURE 5.4 ULTRASTRUCTURE OF TRACHEAL, BRONCHIAL, AND BRONCHIOLAR EPITHELIUM

The respiratory airways are lined by a pseudostratified, ciliated columnar epithelium. In smaller airways the epithelium may become low columnar or simple cuboidal. The ciliated cells constitute approximately 30% of the total cell population. Goblet cells (30% of cell population) secrete mucus that coats the epithelial cells. This mucous coating protects the epithelial cells from desiccation and traps inhaled particulates that are then transported up the airways and out of the lungs by the ciliated cells—a process termed mucociliary transport. Basal cells (30% of cell population) are stem cells that give rise to the goblet, ciliated, and brush cells. The function of brush cells (3% of cell population) is not resolved. They may represent goblet cells that have released their contents, or they may have a sensory role. The Kulchitsky cells (3% of cell population) secrete a number of paracrine factors that likely regulate the function of nearby cells. They are part of the bodies diffuse neuroendocrine system (DNES). Clara cells secrete a surfactant-like material that reduces surface tension of the bronchioles. They may also degrade inhaled toxins. The function of the secretory product of the serous cells is not known.

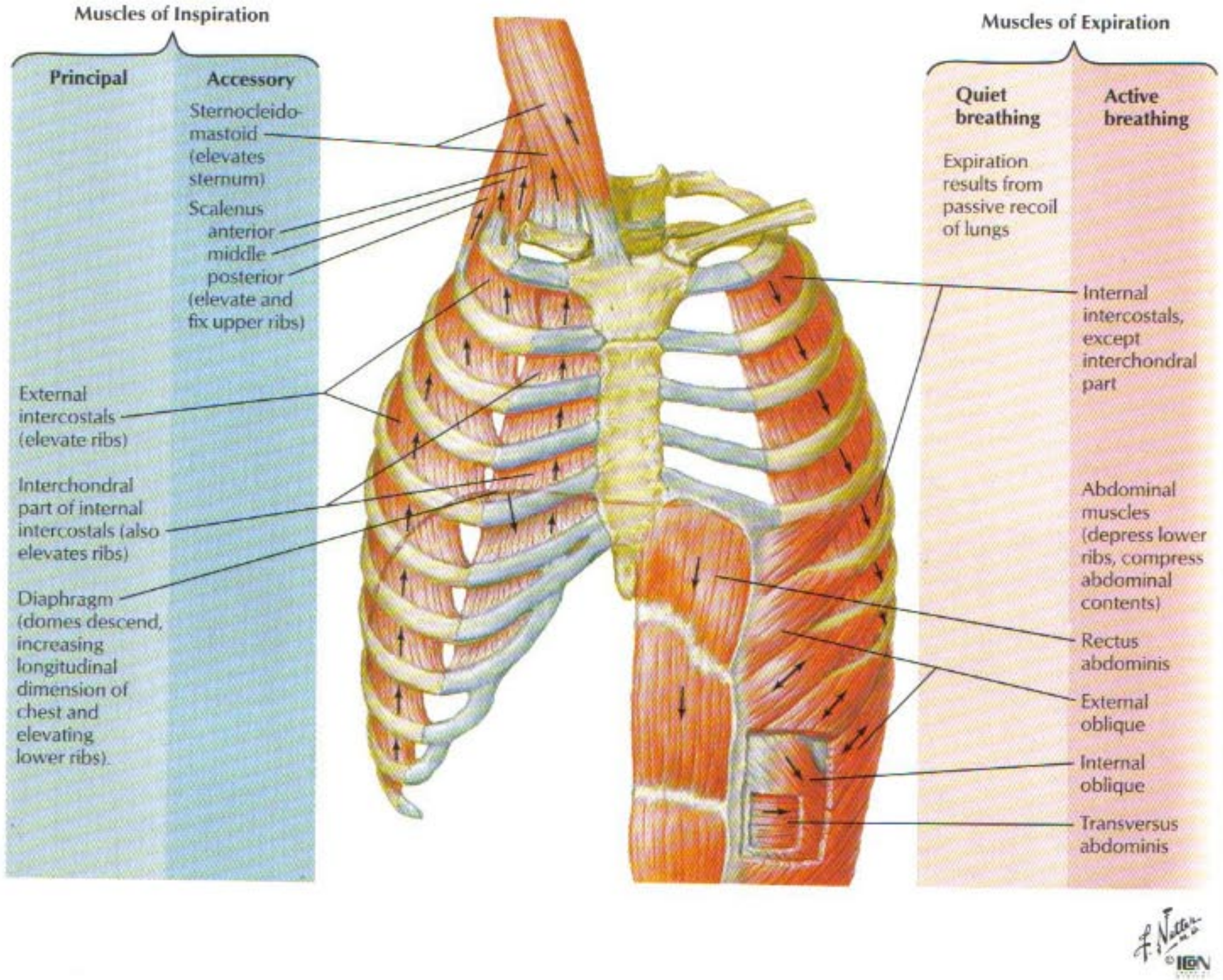

Muscles of Inspiration
Principal
Accessory
Sternocleidomastoid (elevates sternum)
Scalenus
anterior
middle
posterior
(elevate and fix upper ribs)
External intercostals (elevate ribs)
Interchondral part of internal intercostals (also elevates ribs)
Diaphragm (domes descend, increasing longitudinal dimension of chest and elevating lower ribs).
Muscles of Expiration
Quiet breathing
Active breathing
Expiration results from passive recoil of lungs
Internal intercostals, except interchondral part
Abdominal muscles (depress lower ribs, compress abdominal contents)
Rectus abdominis
External oblique
Internal oblique
Transversus abdominis
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FIGURE 5.5 RESPIRATORY MUSCLES

During quiet respiration, contraction of the diaphragm alone accounts for about 75% of inspiration. Muscles of the thoracic wall (intercostal muscles) and selected muscles of the neck and abdomen also can participate in inspiration and assist the diaphragm, especially during active breathing (e.g., during exercise).

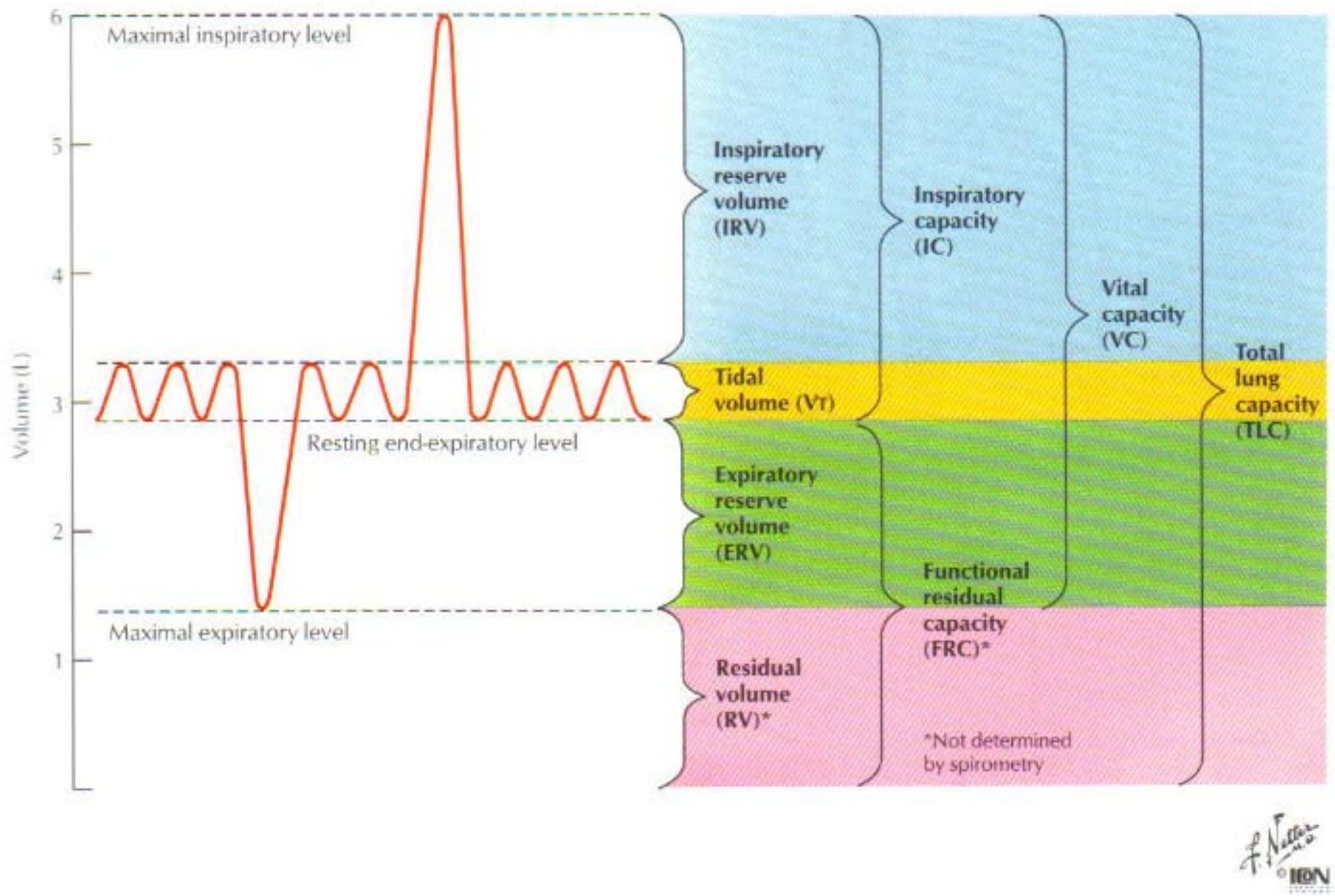


Figure 5.6 Spirometry

Lung volumes are determined by spirometry. Shown are a number of normal tidal breaths, as well as one maximal inspiratory and one maximal expiratory breath. Typical volumes for an adult are shown.

A. At rest

1. Respiratory muscles are at rest
2. Recoil of lung and chest wall are equal but opposite
3. Pressure along tracheobronchial tree is atmospheric
4. There is no airflow

B. During inspiration

Inspiratory muscles contract and chest expands; alveolar pressure becomes subatmospheric with respect to pressure at airway opening. Air flows into lungs

C. During expiration

Inspiratory muscles relax; recoil of lung causes alveolar pressure to exceed pressure at airway opening. Air flows out of lung

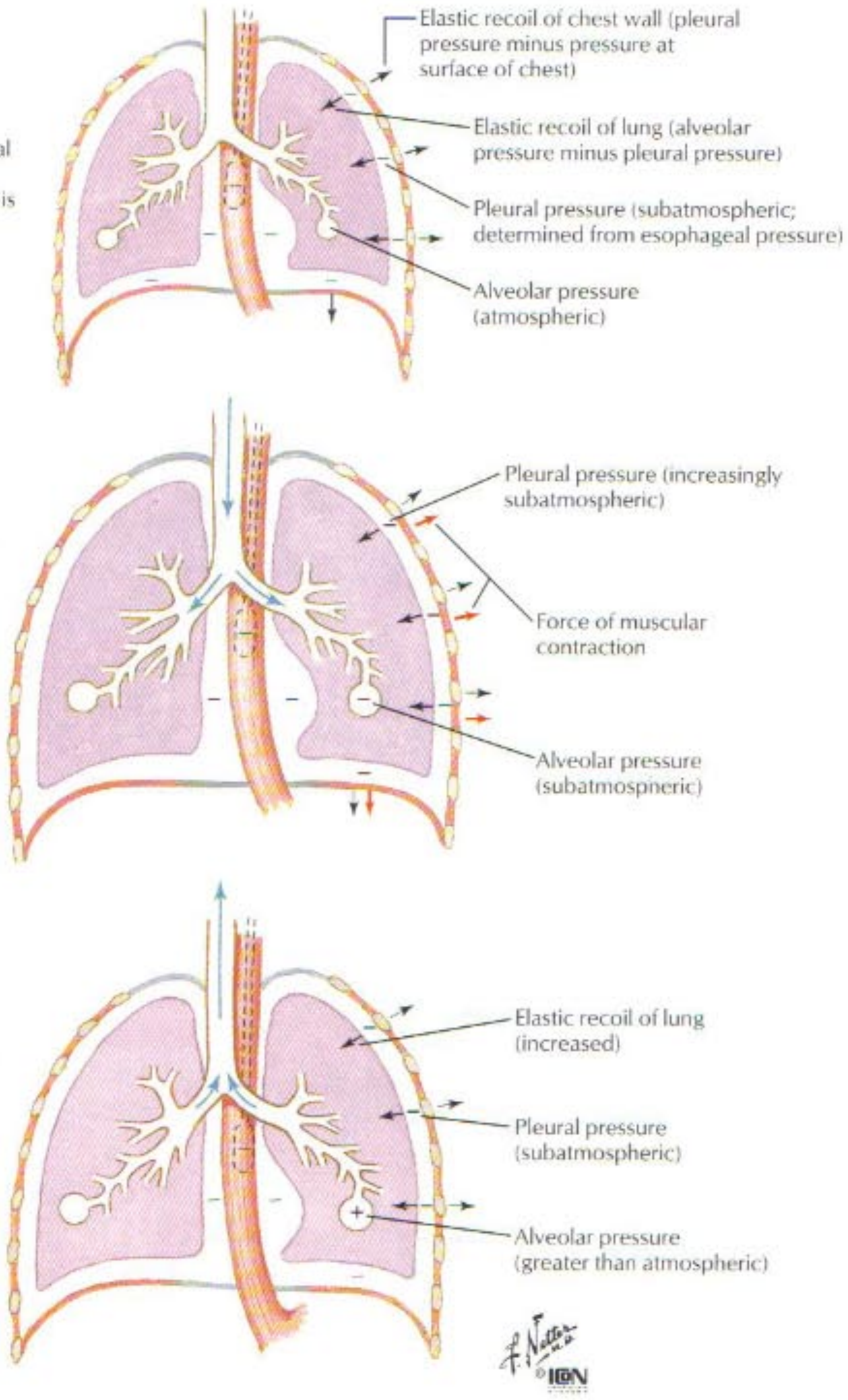
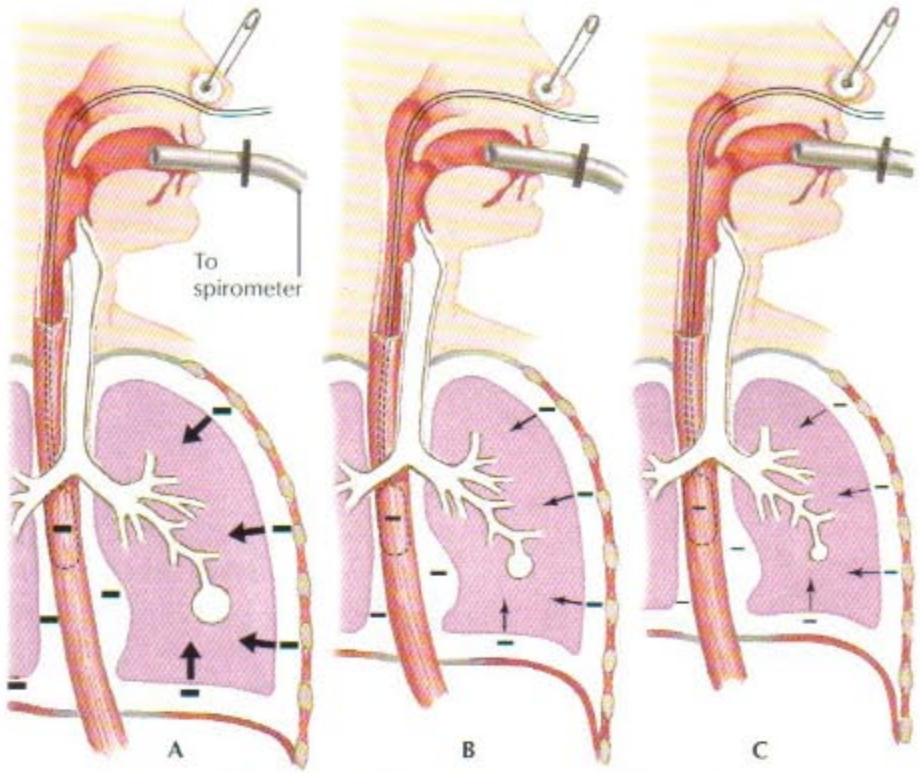

Elastic recoil of chest wall (pleural pressure minus pressure at surface of chest)
Elastic recoil of lung (alveolar pressure minus pleural pressure)
Pleural pressure (subatmospheric; determined from esophageal pressure)
Alveolar pressure (atmospheric)
Pleural pressure (increasingly subatmospheric)
Force of muscular contraction
Alveolar pressure (subatmospheric)
Elastic recoil of lung (increased)
Pleural pressure (subatmospheric)
Alveolar pressure (greater than atmospheric)
+

FIGURE 5.7 FORCES DURING QUIET BREATHING

The mechanics of ventilation involve the dynamic interaction of the lungs, chest wall, and diaphragm. The interplay of these structures and the resulting changes in pleural and alveolar pressures are depicted at rest and during inspiration and expiration.



During a slow expiration from TLC, flow is periodically interrupted and measurements are made of lung volume and of transpulmonary pressure. Transpulmonary pressure is difference between alveolar and pleural pressures. Pleural pressure is determined from pressure in esophagus. Because there is no airflow, alveolar pressure is same as pressure at airway opening

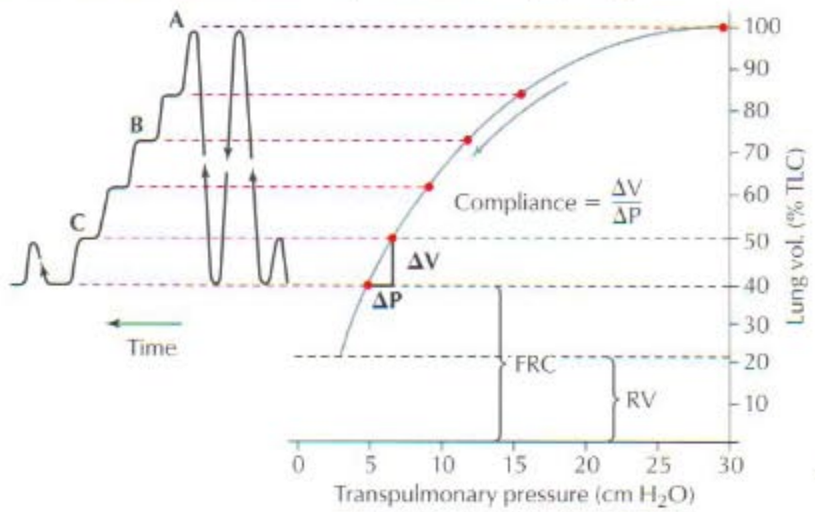
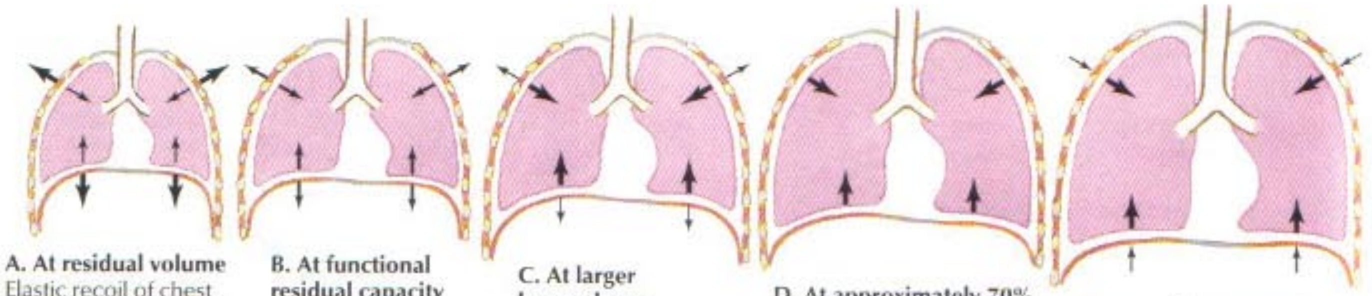


Figure 5.8 Measurement of Elastic Properties of Lung

Compliance is a measure of the elasticity or distensibility of the lung, the chest wall, or the lung and chest wall as a single unit. It is measured as the change in volume resulting from a change in pressure ($\Delta V/\Delta P$). Depicted here is the measurement of the compliance of the lung. To measure lung compliance the change in lung volume is measured as the transpulmonary pressure (alveolar pressure − pleural pressure) varies during expiration. Pleural pressure is measured by a balloon placed in the esophagus.



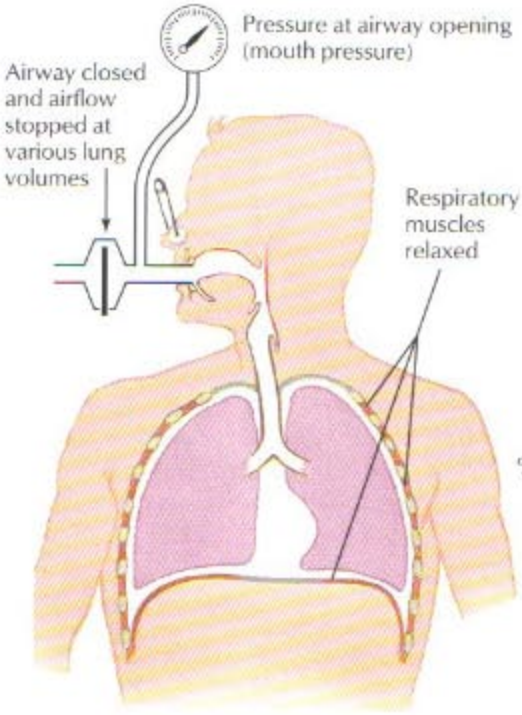
A. At residual volume Elastic recoil of chest wall directed outward is large. Recoil of lung directed inward is very small

B. At functional residual capacity Elastic recoils of lung and chest wall are equal but opposite

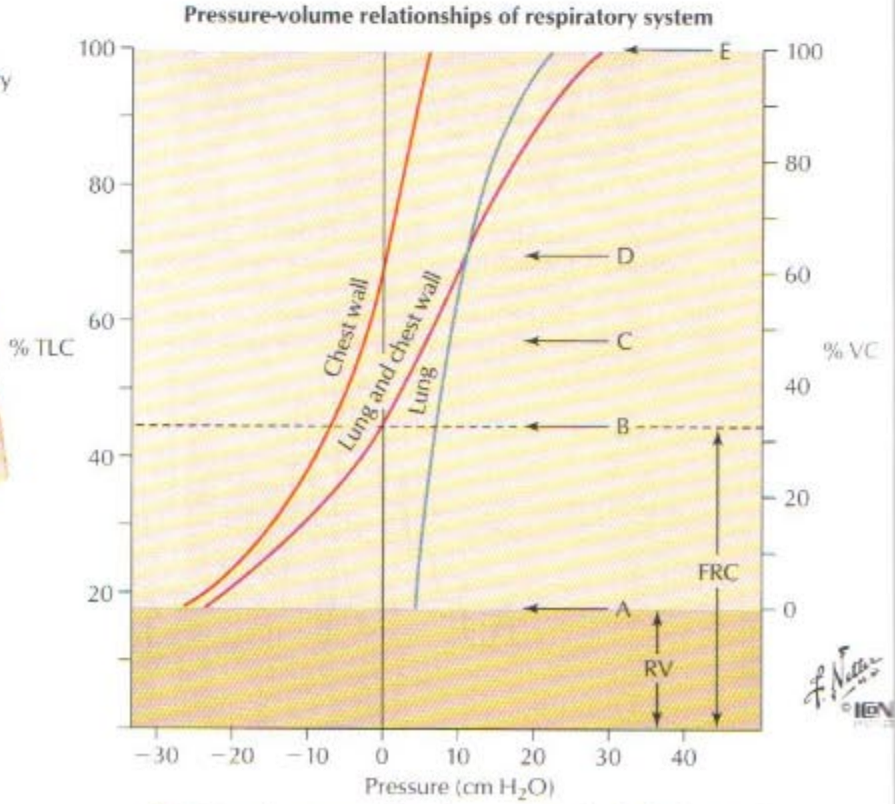
C. At larger lung volume Elastic recoil of chest wall becomes smaller, and recoil of lung increases

D. At approximately 70% of total lung capacity Equilibrium position of chest wall (its recoil equals zero)

E. At total lung capacity Elastic recoil of both lung and chest wall directed inward, favoring decrease in lung volume


Pressure at airway opening (mouth pressure)
Airway closed and airflow stopped at various lung volumes
Respiratory muscles relaxed

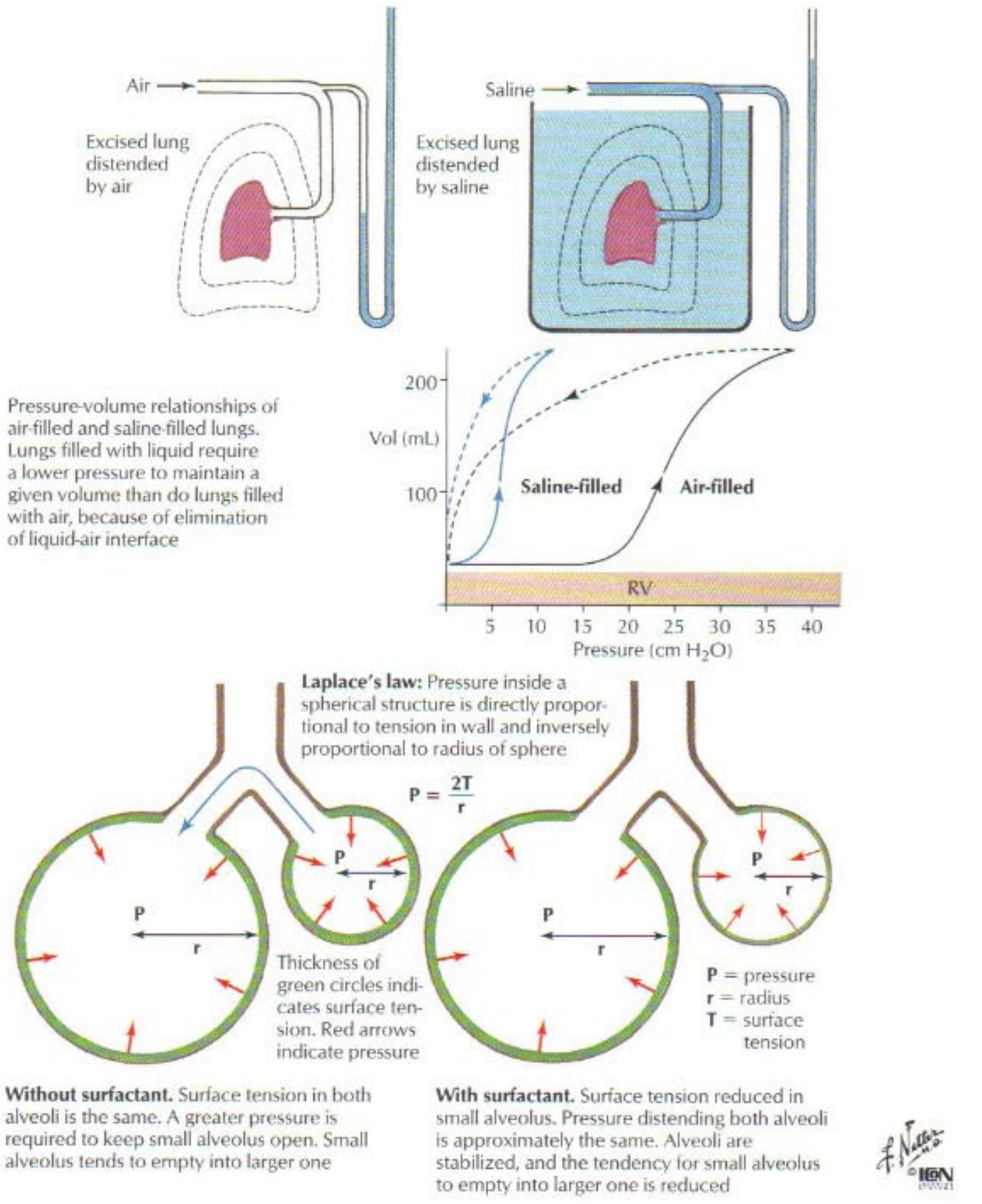
Pressure recorded at airway opening is same as alveolar pressure when airflow is stopped; provides a measure of elastic recoil of respiratory system when respiratory muscles are relaxed



Elastic recoil pressure of respiratory system is algebraic sum of recoil pressures of lung and chest wall

FIGURE 5.9 ELASTIC PROPERTIES OF RESPIRATORY SYSTEM: LUNG AND CHEST WALL

The elastic recoil (or compliance) properties of the lungs and chest wall alone and combined are shown diagrammatically and graphically.


Air
Excised lung distended by air
Saline
Excised lung distended by saline
200
Vol (mL)
100
Saline-filled
Air-filled
RV
5 10 15 20 25 30 35 40
Pressure (cm H_2O)
P
r
P
r
P
r
P
r
P = pressure
r = radius
T = surface tension

Pressure-volume relationships of air-filled and saline-filled lungs. Lungs filled with liquid require a lower pressure to maintain a given volume than do lungs filled with air, because of elimination of liquid-air interface

Laplace's law: Pressure inside a spherical structure is directly proportional to tension in wall and inversely proportional to radius of sphere

$$P = \frac{2T}{r}$$

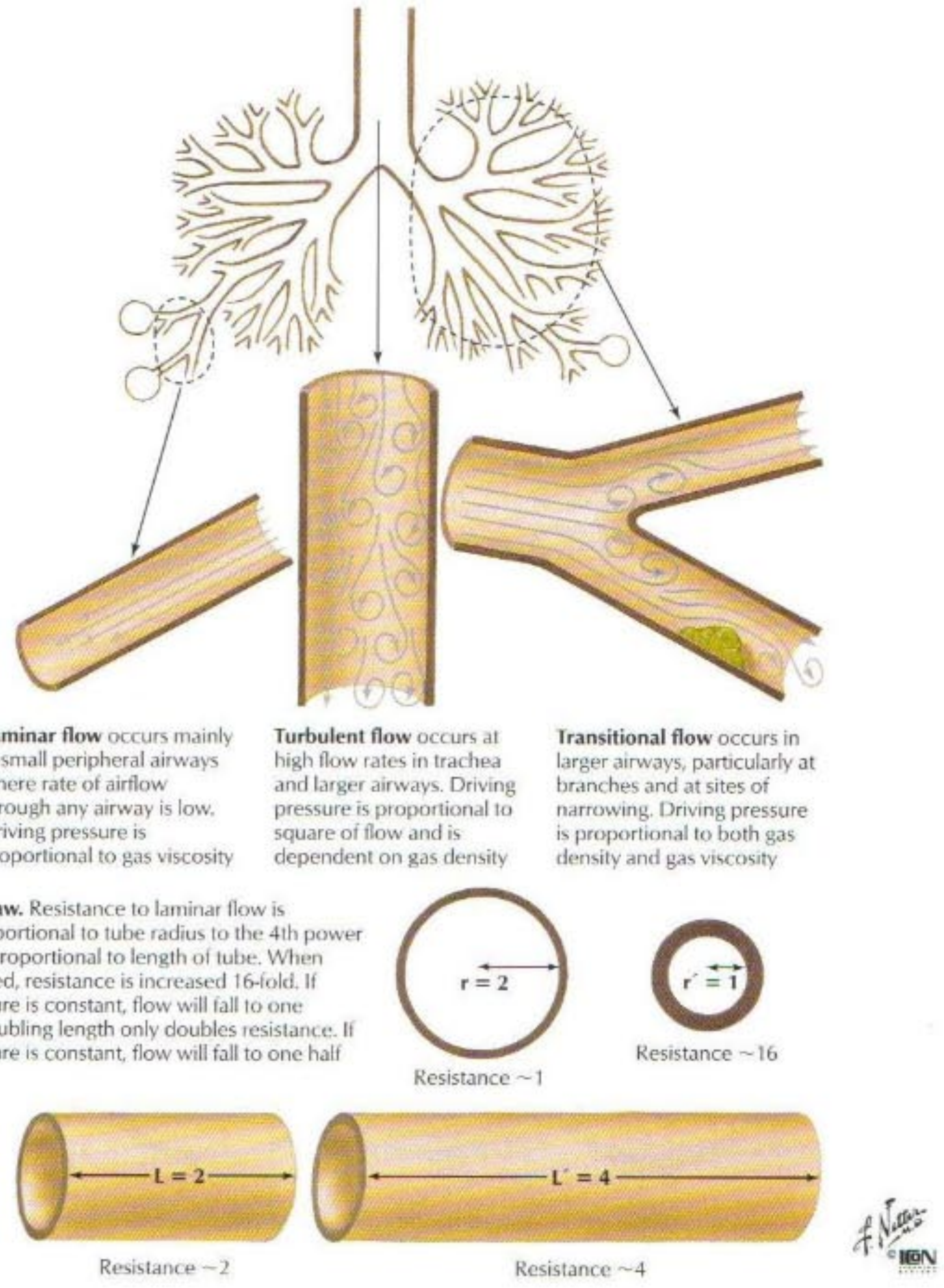
Thickness of green circles indicates surface tension. Red arrows indicate pressure

Without surfactant. Surface tension in both alveoli is the same. A greater pressure is required to keep small alveolus open. Small alveolus tends to empty into larger one

With surfactant. Surface tension reduced in small alveolus. Pressure distending both alveoli is approximately the same. Alveoli are stabilized, and the tendency for small alveolus to empty into larger one is reduced

FIGURE 5.10 SURFACE FORCES IN THE LUNG

The alveoli are coated with a thin film of surfactant (lipoprotein produced by type 2 alveolar cells). Surfactant reduces the surface tension that exists at the air-alveolar interface. This has several effects, including a decrease in elastic recoil of the lung, an increase in lung compliance, and a decrease in the work required to inflate the lung during inspiration. Surfactants' effect on surface tension is greater in small alveoli compared with large alveoli. This tends to stabilize the alveoli and thereby equalize alveolar pressures throughout the lung.



Laminar flow occurs mainly in small peripheral airways where rate of airflow through any airway is low. Driving pressure is proportional to gas viscosity

Turbulent flow occurs at high flow rates in trachea and larger airways. Driving pressure is proportional to square of flow and is dependent on gas density

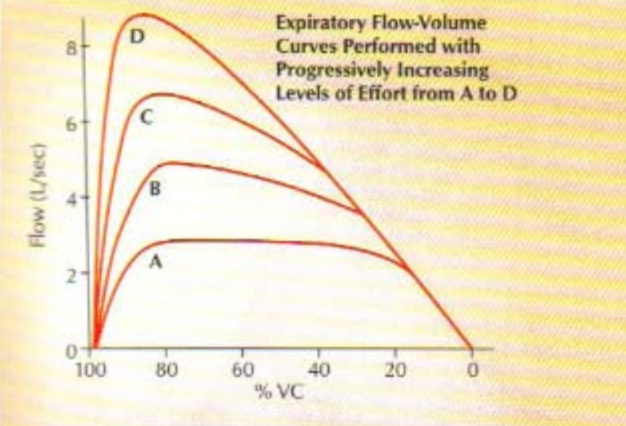
Transitional flow occurs in larger airways, particularly at branches and at sites of narrowing. Driving pressure is proportional to both gas density and gas viscosity

Poiseuille's law. Resistance to laminar flow is inversely proportional to tube radius to the 4th power and directly proportional to length of tube. When radius is halved, resistance is increased 16-fold. If driving pressure is constant, flow will fall to one sixteenth. Doubling length only doubles resistance. If driving pressure is constant, flow will fall to one half

FIGURE 5.11 AIRWAY FLOW

Airflow through the large airways of the lung is turbulent and therefore can be heard with a stethoscope (i.e., breath sounds). Laminar flow occurs only in the small airways. The major factor that determines resistance to airflow is the diameter of the airway, because resistance varies as the fourth power of the radius.

FACOLTA' DI MEDICINA E CHIRURGIA

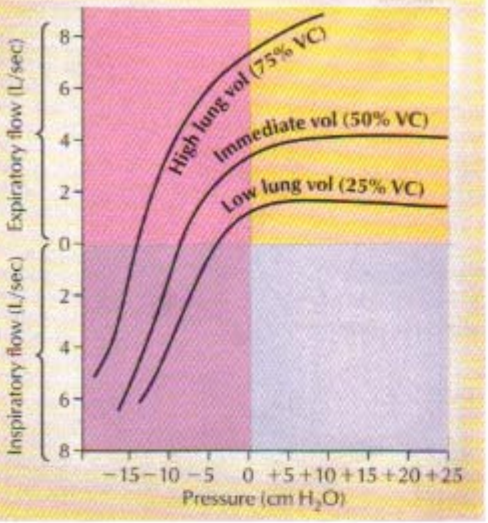


Expiratory Flow-Volume Curves Performed with Progressively Increasing Levels of Effort from A to D

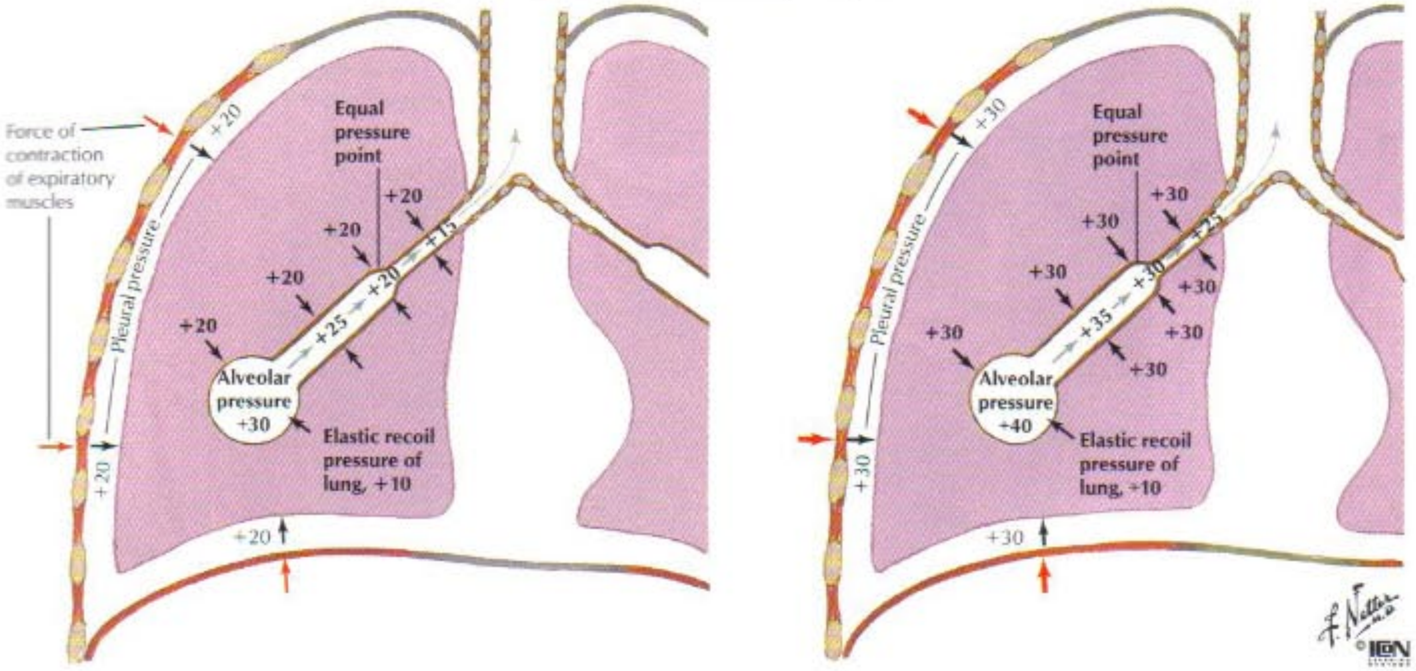
At high lung volumes, rate of airflow during expiration increases progressively with increasing effort. At intermediate and low lung volumes, airflow reaches maximal levels after only modest effort is exerted and thereafter increases no further despite increasing effort

Isovolume Pressure-Flow Curves

At lung volumes greater than 75% of VC, airflow increases progressively with increasing pleural pressure. Airflow is effort dependent. At volumes below 75% of VC, airflow levels off as pleural pressure exceeds atmospheric pressure. Thereafter, airflow is effort independent, because further increases in pleural pressure result in no further rise in rate of airflow



Determinants of Maximal Expiratory Flow


Force of contraction of expiratory muscles
+20
Equal pressure point
+20
+20
+20
+15
+20
+20
+25
+20
Alveolar pressure +30
Elastic recoil pressure of lung, +10
Pleural pressure
+20
+20
+30
Equal pressure point
+30
+30
+30
+25
+30
+30
+30
+35
+30
+30
+30
Alveolar pressure +40
Elastic recoil pressure of lung, +10
Pleural pressure
+30
+30
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At onset of maximal airflow contraction of expiratory muscles at a given lung volume raises pleural pressure above atmospheric level (+20 cm H_2O). Alveolar pressure (sum of pleural pressure and lung recoil pressure) is yet higher (+30 cm H_2O). Airway pressure falls progressively from alveolus to airway opening in overcoming resistance. At equal pressure point of airway, pressure within airway equals pressure surrounding it (pleural pressure). Beyond this point, as intraluminal pressure drops further, below pleural pressure, airway will be compressed

With further increases in expiratory effort, at same lung volume, pleural pressure is greater and alveolar pressure is correspondingly higher. Fall in airway pressure and location of equal pressure point are unchanged, but beyond equal pressure point, intrathoracic airways will be compressed to a greater degree by higher pleural pressure. Once maximal airflow is achieved, further increases in pleural pressure produce proportional increases in resistance of segment downstream from equal pressure point, so rate of airflow does not change

FIGURE 5.12 FLOW-VOLUME RELATIONSHIPS

Airflow varies as a function of pressure and lung volume. The highest rates of airflow are seen at high lung volumes.

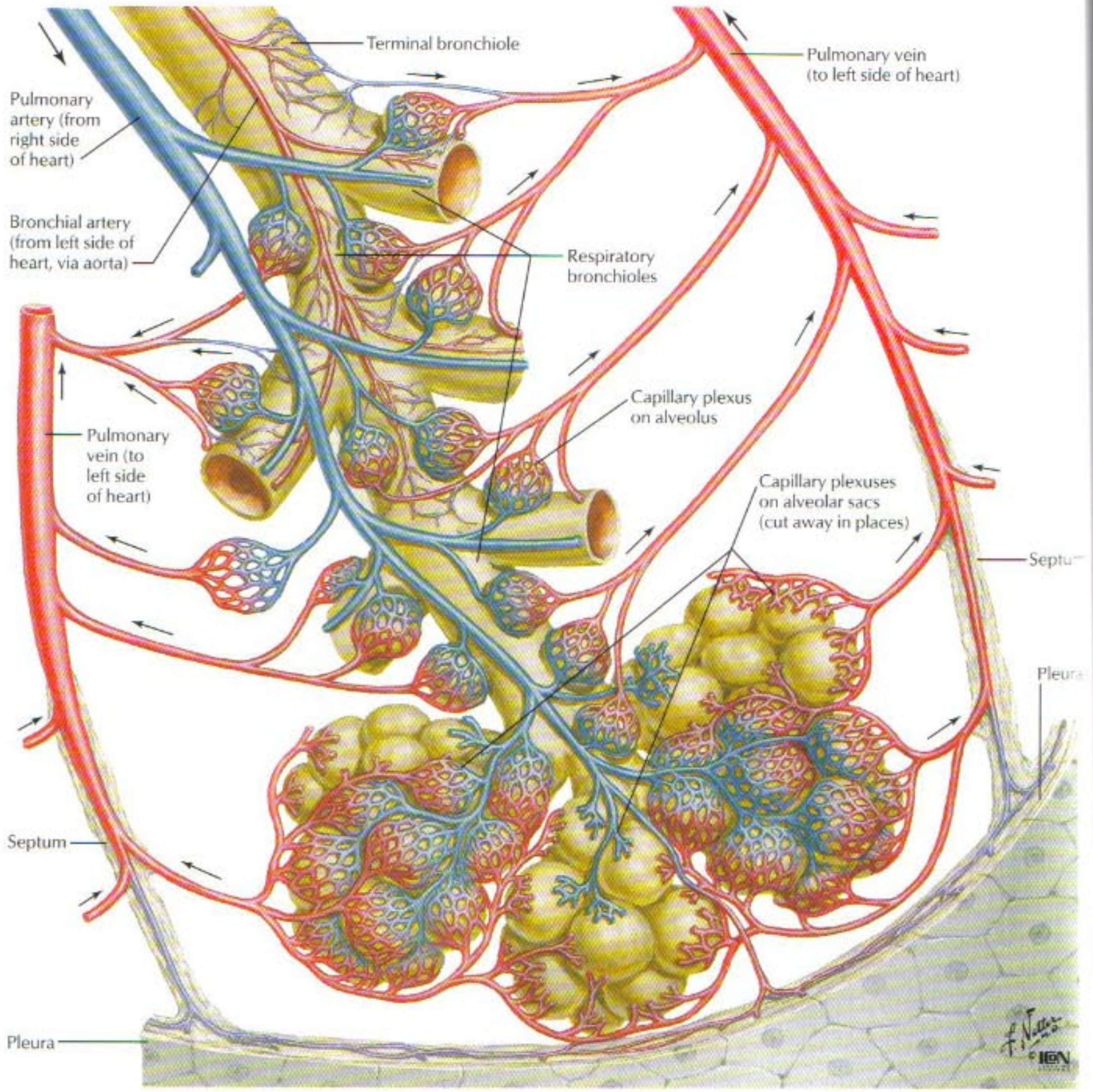

Terminal bronchiole
Pulmonary vein (to left side of heart)
Pulmonary artery (from right side of heart)
Bronchial artery (from left side of heart, via aorta)
Respiratory bronchioles
Capillary plexus on alveolus
Pulmonary vein (to left side of heart)
Capillary plexuses on alveolar sacs (cut away in places)
Septu
Pleur
Septum
Pleura

FIGURE 5.13 INTRAPULMONARY BLOOD CIRCULATION

Blood from the right ventricle of the heart perfuses the lungs (via the pulmonary artery) at a relatively high rate (approximately 5 L/min) but under low pressure (driving pressure of about 6 mm Hg). Pulmonary capillary plexuses envelop the alveolar sacs, where most of the gas exchange occurs. Pulmonary veins collect the oxygenated blood and return it to the left side of the heart for distribution to the systemic circulation. In a normal resting adult, the lungs contain about 75 mL of blood distributed variably across its vasculature.

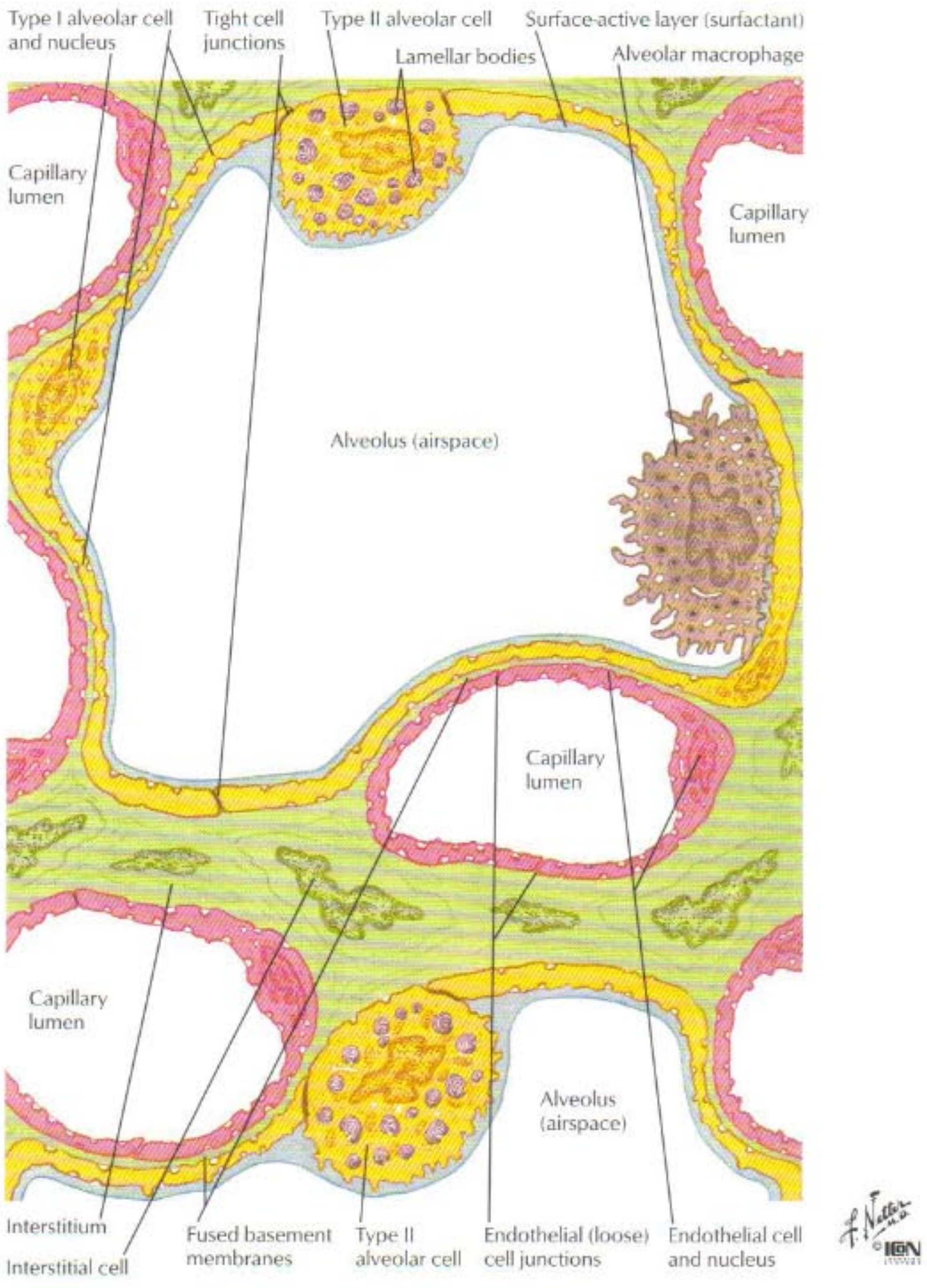
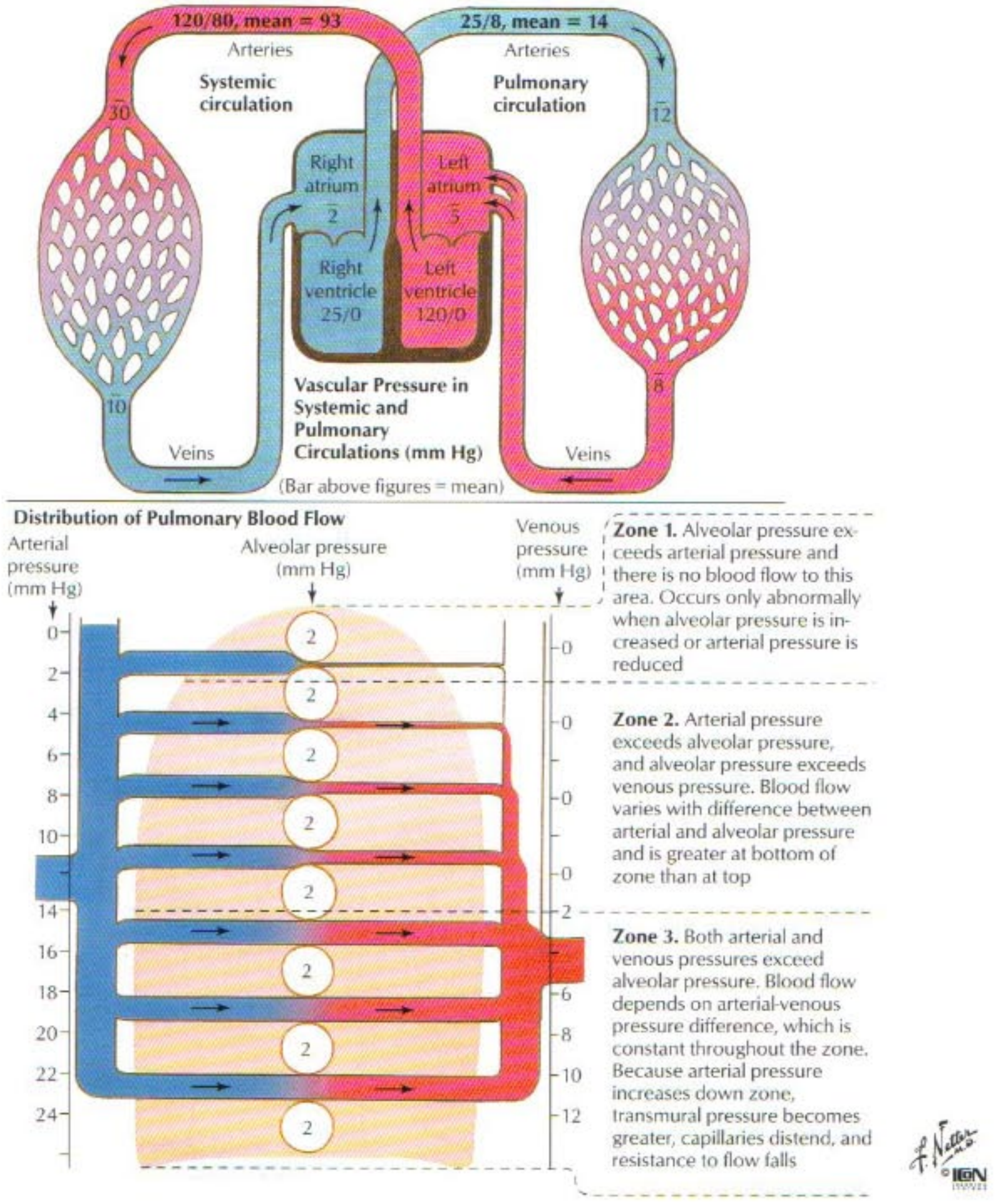

Type I alveolar cell and nucleus
Tight cell junctions
Type II alveolar cell
Surface-active layer (surfactant)
Lamellar bodies
Alveolar macrophage
Capillary lumen
Capillary lumen
Alveolus (airspace)
Capillary lumen
Capillary lumen
Alveolus (airspace)
Interstitium
Interstitial cell
Fused basement membranes
Type II alveolar cell
Endothelial (loose) cell junctions
Endothelial cell and nucleus

FIGURE 5.14 ULTRASTRUCTURE OF PULMONARY ALVEOLI AND CAPILLARIES

Gas exchange occurs across the type I alveolar cells, the basement membrane, and the capillary endothelial cell. The type II alveolar cells secrete surfactant, which forms a thin layer over the fluid that coats the surface of the alveolus. Alveolar macrophages migrate out of the capillaries and can be found in the interstitium of the alveolar septa or within the alveolus itself. They serve to engulf inhaled particulates and bacteria.


120/80, mean = 93
Arteries
Systemic circulation
25/8, mean = 14
Arteries
Pulmonary circulation
30
12
Right atrium
2
Left atrium
5
Right ventricle 25/0
Left ventricle 120/0
10
8
Veins
Veins
Arterial pressure (mm Hg)
Alveolar pressure (mm Hg)
Venous pressure (mm Hg)
0
2
4
6
8
10
14
16
18
20
22
24
2
0
0
0
0
2
6
8
10
12

Vascular Pressure in Systemic and Pulmonary Circulations (mm Hg)

(Bar above figures = mean)

Distribution of Pulmonary Blood Flow

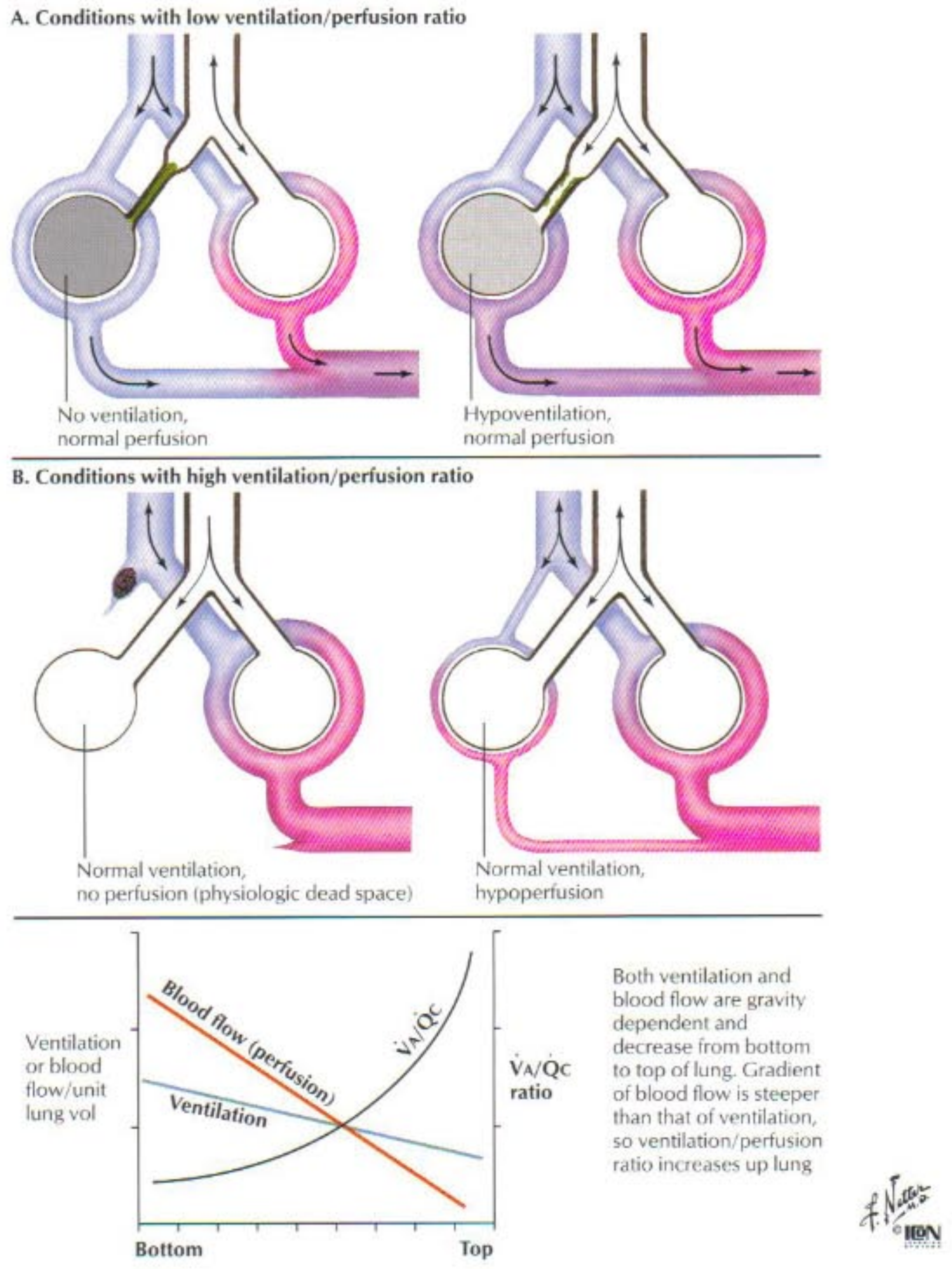
Zone 1. Alveolar pressure exceeds arterial pressure and there is no blood flow to this area. Occurs only abnormally when alveolar pressure is increased or arterial pressure is reduced

Zone 2. Arterial pressure exceeds alveolar pressure, and alveolar pressure exceeds venous pressure. Blood flow varies with difference between arterial and alveolar pressure and is greater at bottom of zone than at top

Zone 3. Both arterial and venous pressures exceed alveolar pressure. Blood flow depends on arterial-venous pressure difference, which is constant throughout the zone. Because arterial pressure increases down zone, transmural pressure becomes greater, capillaries distend, and resistance to flow falls

FIGURE 5.15 PULMONARY CIRCULATION

Due to the effects of gravity, blood flow is not evenly distributed throughout the lung. As a result, the capillaries in the apex of the lung are almost completely collapsed and blood flow through them is minimal, but still occurs. Flow is absent if alveolar pressure is increased (e.g., positive-pressure ventilation) or arterial pressure is decreased (e.g., hemorrhage).



A. Conditions with low ventilation/perfusion ratio

No ventilation,
normal perfusion
Hypoventilation,
normal perfusion

B. Conditions with high ventilation/perfusion ratio

Normal ventilation,
no perfusion (physiologic dead space)
Normal ventilation,
hypoperfusion
Ventilation or blood flow/unit lung vol
Blood flow (perfusion)
Ventilation
$\dot{V}_A/\dot{Q}_C$
$\dot{V}_A/\dot{Q}_C$ ratio
Bottom
Top

Both ventilation and blood flow are gravity dependent and decrease from bottom to top of lung. Gradient of blood flow is steeper than that of ventilation, so ventilation/perfusion ratio increases up lung

Figure 5.16 Ventilation/Perfusion ($\dot{V}a/\dot{Q}c$) Relationships

Gravity affects not only capillary perfusion (see Figure 5.15) but alveolar ventilation as well. In an erect person the ratio of ventilation to perfusion (Va/Qc) is greater than 1 at the apices (i.e., high ventilation but low blood flow), whereas the opposite is true at the bases. In a normal lung the average Va/Qc is approximately 1.

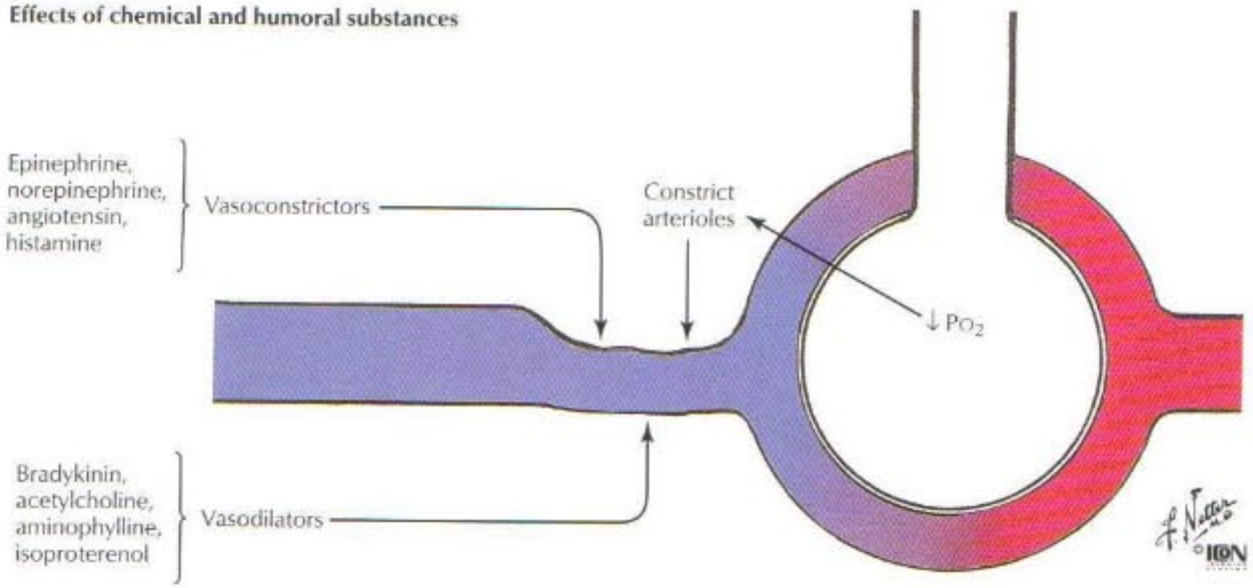

Effects of chemical and humoral substances
Epinephrine,
norepinephrine,
angiotensin,
histamine
Vasoconstrictors
Constrict
arterioles
↓ P_{O_2}
Bradykinin,
acetylcholine,
aminophylline,
isoproterenol
Vasodilators

FIGURE 5.17 PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance is influenced by a number of substances. Importantly, a decrease in alveolar P_{O_2} constricts the arterioles perfusing that alveolus. This is in contrast to all other vascular beds in the body, where a decrease on P_{O_2} dilates arterioles. This unique response of the pulmonary arterioles to a decrease in alveolar P_{O_2} helps ensure that the capillaries of nonaerated alveoli are not perfused.

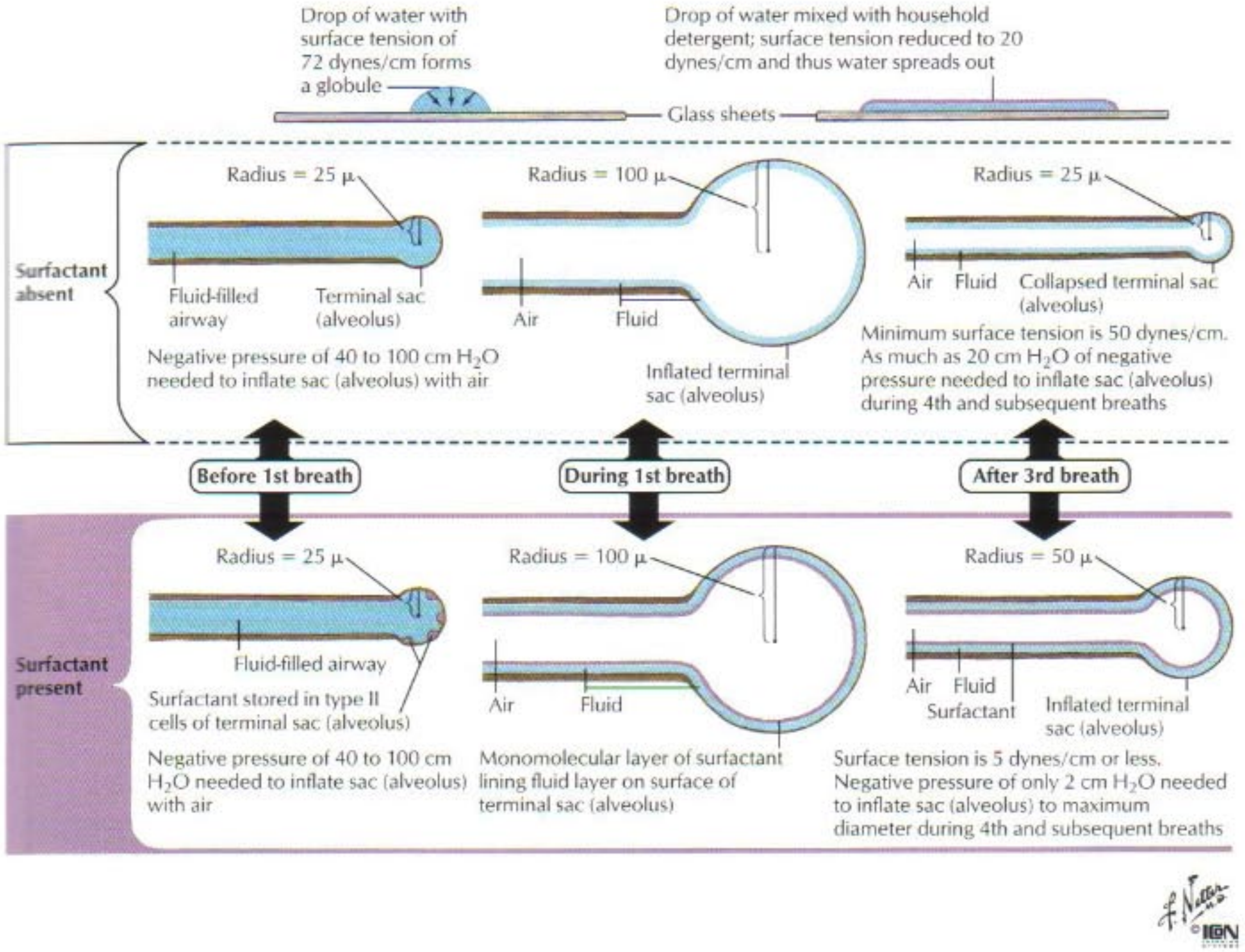

Drop of water with surface tension of 72 dynes/cm forms a globule
Drop of water mixed with household detergent; surface tension reduced to 20 dynes/cm and thus water spreads out
Glass sheets
Surfactant absent
Radius = 25 μ
Fluid-filled airway
Terminal sac (alveolus)
Negative pressure of 40 to 100 cm H_2O needed to inflate sac (alveolus) with air
Radius = 100 μ
Air
Fluid
Inflated terminal sac (alveolus)
Radius = 25 μ
Air
Fluid
Collapsed terminal sac (alveolus)
Minimum surface tension is 50 dynes/cm. As much as 20 cm H_2O of negative pressure needed to inflate sac (alveolus) during 4th and subsequent breaths
Before 1st breath
During 1st breath
After 3rd breath
Surfactant present
Radius = 25 μ
Fluid-filled airway
Surfactant stored in type II cells of terminal sac (alveolus)
Negative pressure of 40 to 100 cm H_2O needed to inflate sac (alveolus) with air
Radius = 100 μ
Air
Fluid
Monomolecular layer of surfactant lining fluid layer on surface of terminal sac (alveolus)
Radius = 50 μ
Air
Fluid
Surfactant
Inflated terminal sac (alveolus)
Surface tension is 5 dynes/cm or less. Negative pressure of only 2 cm H_2O needed to inflate sac (alveolus) to maximum diameter during 4th and subsequent breaths
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FIGURE 5.18 SURFACTANT EFFECTS

Surfactant is produced by type II alveolar cells (see Figure 5.14). Its major component is the phospholipid dipalmitoyl phosphatidylcholine. It acts to reduce the surface tension of the fluid-lined alveoli (see also Figure 5.10). Thus, lower pressures are required to inflate the alveoli. Failure to produce sufficient amounts of surfactant, as can occur in premature infants, results in an increase in the work of breathing and respiratory distress.

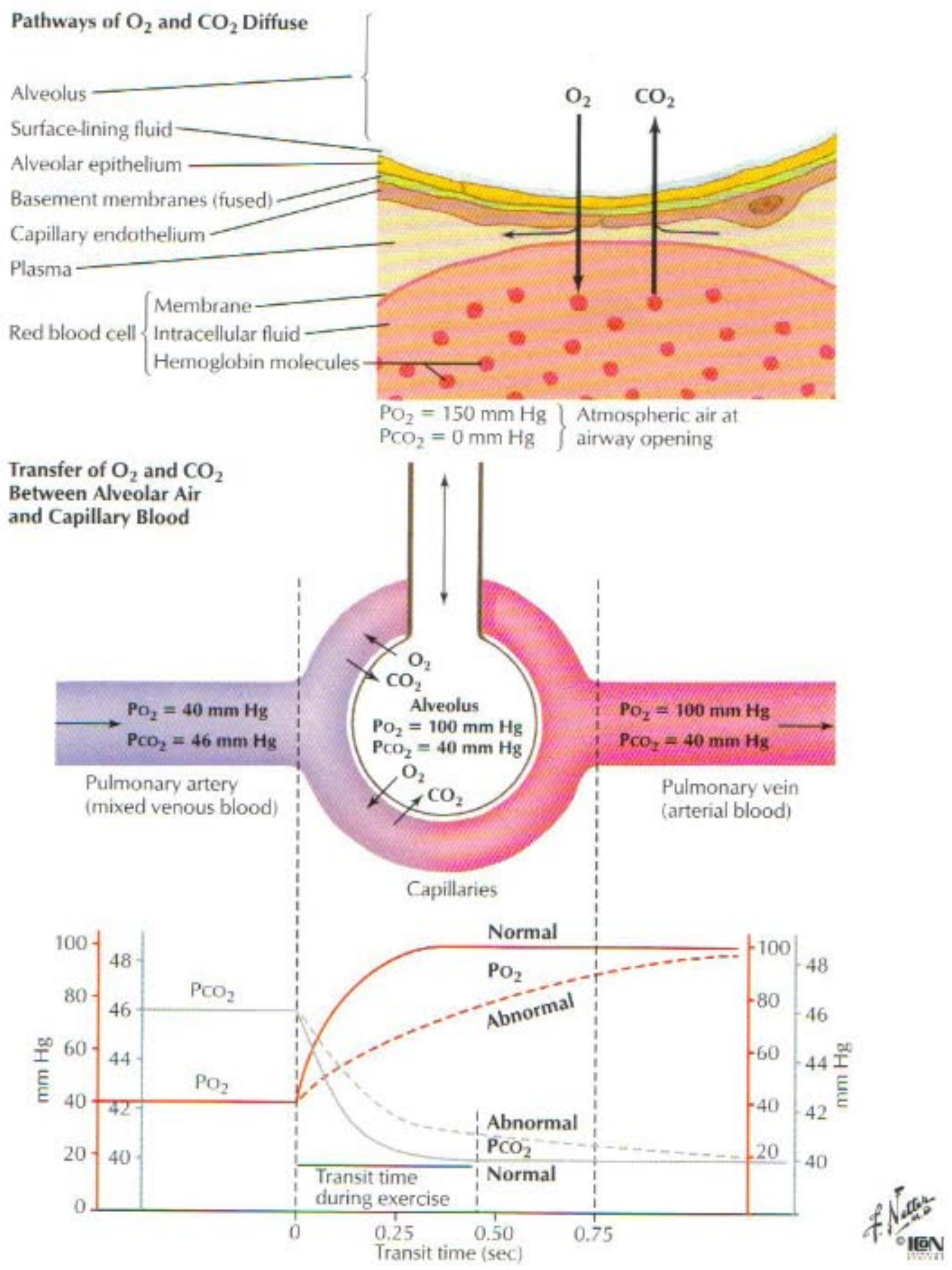
Pathways of O_2 and CO_2 Diffuse
Alveolus
Surface-lining fluid
Alveolar epithelium
Basement membranes (fused)
Capillary endothelium
Plasma
Red blood cell
Membrane
Intracellular fluid
Hemoglobin molecules
O_2
CO_2
P_{O_2} = 150 mm Hg
P_{CO_2} = 0 mm Hg
Atmospheric air at airway opening
Transfer of O_2 and CO_2 Between Alveolar Air and Capillary Blood
O_2
CO_2
Alveolus
P_{O_2} = 100 mm Hg
P_{CO_2} = 40 mm Hg
O_2
CO_2
P_{O_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
Pulmonary artery (mixed venous blood)
P_{O_2} = 100 mm Hg
P_{CO_2} = 40 mm Hg
Pulmonary vein (arterial blood)
Capillaries
mm Hg
100
80
60
40
20
0
48
46
44
42
40
P_{CO_2}
P_{O_2}
Normal
P_{O_2}
Abnormal
Abnormal
P_{CO_2}
Normal
Transit time during exercise
0
0.25
0.50
0.75
Transit time (sec)
100
80
60
40
20
48
46
44
42
40
mm Hg
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FIGURE 5.19 O_2 AND CO_2 EXCHANGE

As blood flows through the alveolar capillary, O_2 diffuses from the alveolus into the red blood cell, where it binds to hemoglobin. At the same time, CO_2 diffuses out of the red blood cell and into the alveolus. Normally, blood traverses the entire length of the capillary in 0.75 second. With increased cardiac output, the transit time is reduced. Full equilibration of blood with alveolar O_2 and CO_2 still occurs with transit times as low as 0.5 second. In some disease stat there is thickening of the alveolar-capillary wall. This restricts the di fusion of O_2 and CO_2 and can prevent full equilibration of blood w the alveolar gases during the time required for the blood to travel th length of the capillary (dashed lines labeled as abnormal).

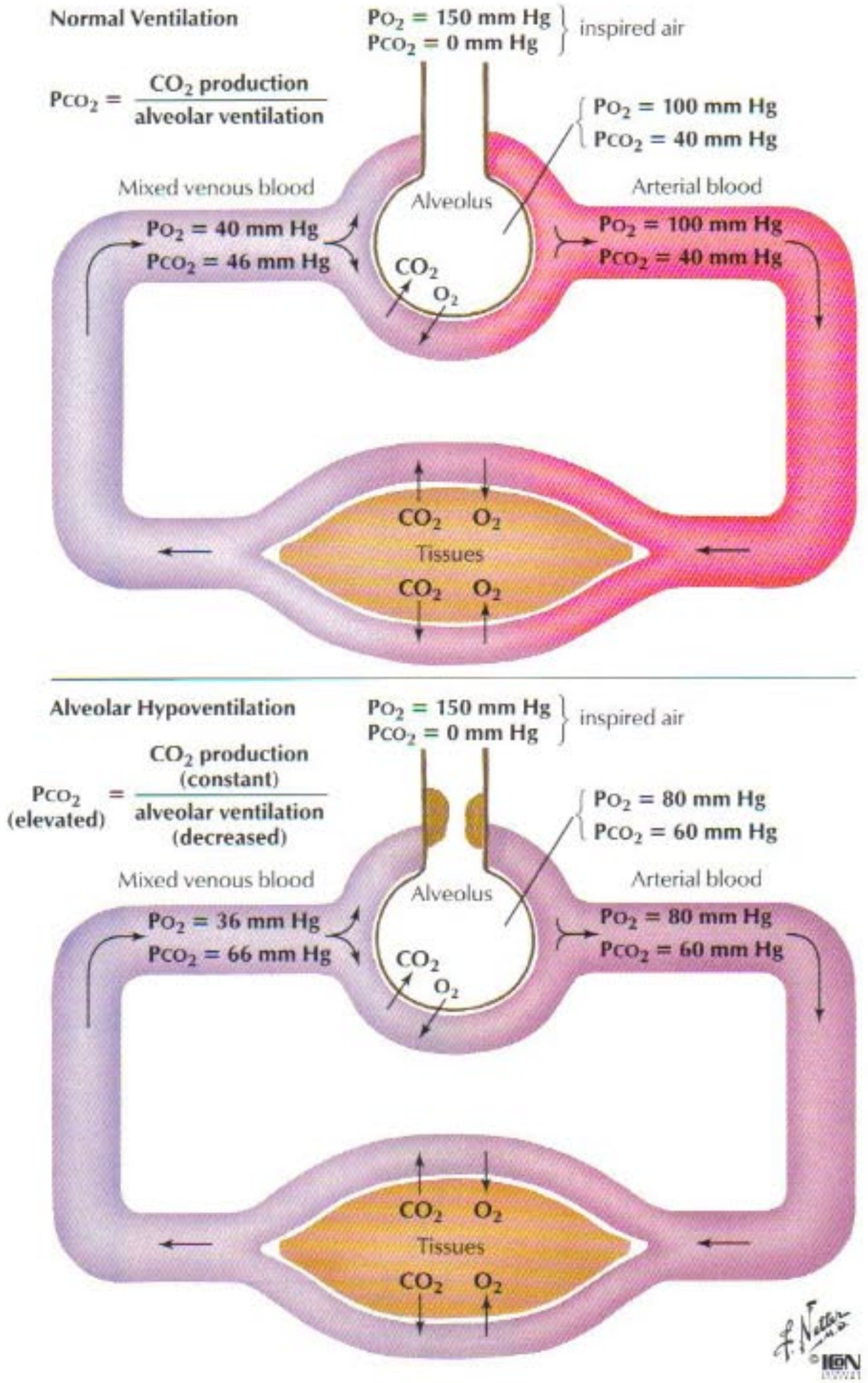
Normal Ventilation
PO_2 = 150 mm Hg
PCO_2 = 0 mm Hg
inspired air
$PCO_2 = \frac{CO_2 \text{ production}}{\text{alveolar ventilation}}$
PO_2 = 100 mm Hg
PCO_2 = 40 mm Hg
Mixed venous blood
Alveolus
Arterial blood
PO_2 = 40 mm Hg
PCO_2 = 46 mm Hg
CO_2
O_2
PO_2 = 100 mm Hg
PCO_2 = 40 mm Hg
CO_2 O_2
Tissues
CO_2 O_2
Alveolar Hypoventilation
PO_2 = 150 mm Hg
PCO_2 = 0 mm Hg
inspired air
PCO_2 (elevated) = $\frac{CO_2 \text{ production (constant)}}{\text{alveolar ventilation (decreased)}}$
PO_2 = 80 mm Hg
PCO_2 = 60 mm Hg
Mixed venous blood
Alveolus
Arterial blood
PO_2 = 36 mm Hg
PCO_2 = 66 mm Hg
CO_2
O_2
PO_2 = 80 mm Hg
PCO_2 = 60 mm Hg
CO_2 O_2
Tissues
CO_2 O_2
F. Netter
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FIGURE 5.20 O_2 AND CO_2 EXCHANGE AND TRANSPORT

Alveolar hypoventilation, illustrated here as a partial blockage of the airway, reduces the alveolar Po_2 and increases the alveolar Pco_2. As a result, the arterial blood Po_2 declines (hypoxia) and the arterial blood Pco_2 increases (hypercapnia).

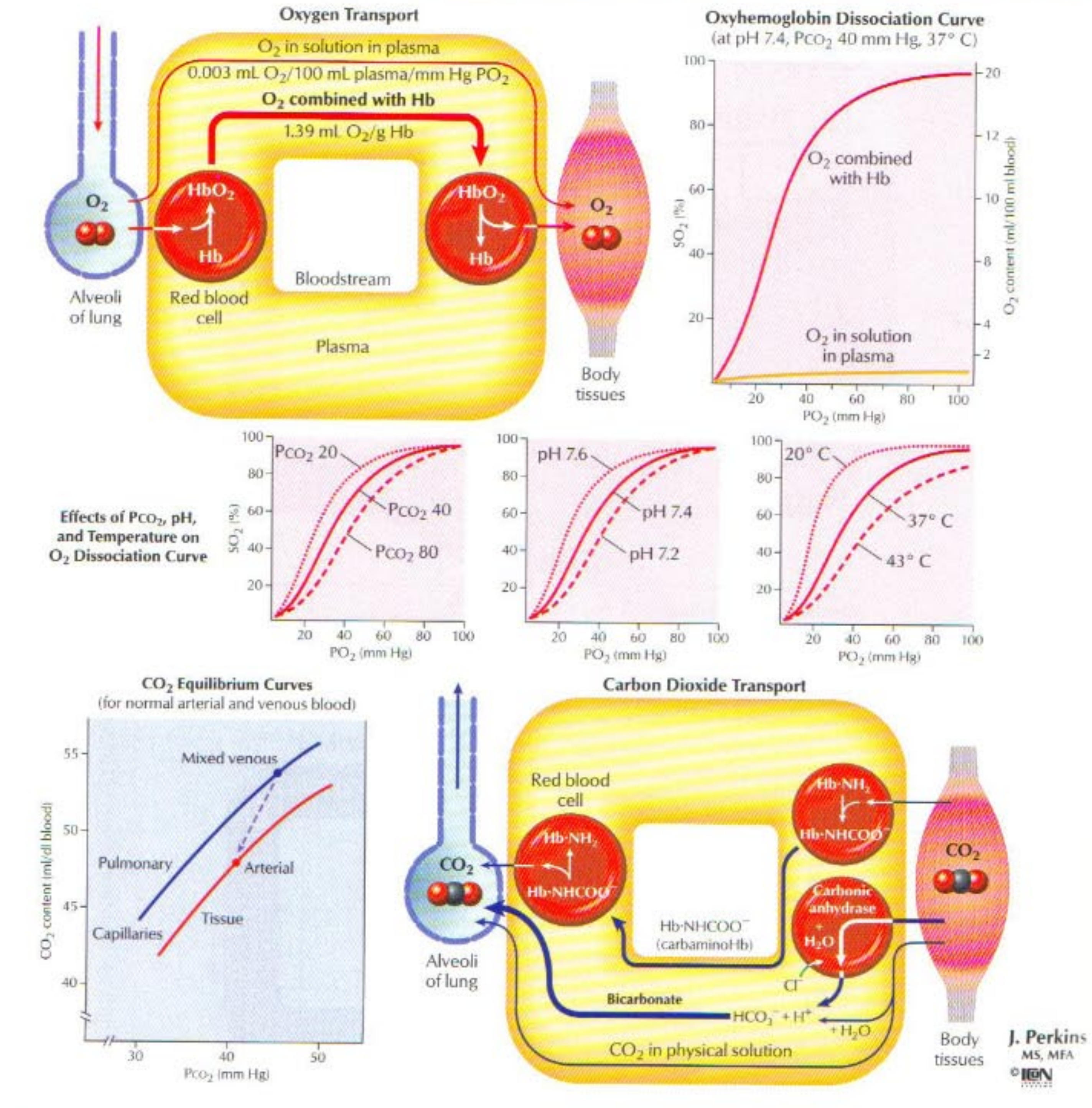
Oxygen Transport
O_2 in solution in plasma
0.003 mL O_2/100 mL plasma/mm Hg PO_2
O_2 combined with Hb
1.39 mL O_2/g Hb
O_2
HbO_2
Hb
HbO_2
Hb
O_2
Bloodstream
Alveoli of lung
Red blood cell
Plasma
Body tissues
Oxyhemoglobin Dissociation Curve
(at pH 7.4, Pco_2 40 mm Hg, 37° C)
SO_2 (%)
100
80
60
40
20
O_2 combined with Hb
O_2 in solution in plasma
20
40
60
80
100
PO_2 (mm Hg)
20
12
10
8
4
2
O_2 content (ml/100 ml blood)
Effects of Pco_2, pH, and Temperature on O_2 Dissociation Curve
Pco_2 20
Pco_2 40
Pco_2 80
pH 7.6
pH 7.4
pH 7.2
20° C
37° C
43° C
SO_2 (%)
PO_2 (mm Hg)
CO_2 Equilibrium Curves
(for normal arterial and venous blood)
55
50
45
40
Mixed venous
Pulmonary
Arterial
Tissue
Capillaries
CO_2 content (ml/dl blood)
30
40
50
Pco_2 (mm Hg)
Carbon Dioxide Transport
Red blood cell
CO_2
Hb·NH_2
Hb·$NHCOO^-$
Hb·NH_2
Hb·$NHCOO^-$
CO_2
Carbonic anhydrase
+
H_2O
Hb·$NHCOO^-$
(carbaminoHb)
Cl^-
Bicarbonate
$HCO_3^- + H^+$
$+H_2O$
CO_2 in physical solution
Alveoli of lung
Body tissues
J. Perkins
MS, MFA
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FIGURE 5.21 O_2/CO_2 EXCHANGE

During each breath, O_2 and CO_2 are exchanged across the alveolar-pulmonary capillary membrane (see Figure 5.19). Almost all of the O_2 carried to the tissues is bound to hemoglobin (Hb); only a small amount is dissolved and transported in plasma. As shown in the oxyhemoglobin dissociation curve, the binding of O_2 to Hb is dependent on the partial pressure of O_2 (Po_2). The percent saturation of Hb (So_2) is about 97.5% when the Po_2 is 100 mm Hg. In the three middle panels, the effects of CO_2, pH, and temperature on the oxyhemoglobin dissociation curve are shown. Hb binding of O_2 is decreased, and thereby off-loading of O_2 to the tissues is increased by increased Pco_2 (hypercapnia), decreased pH (acidosis), or increased body temperature (fever). CO_2 from the tissues is transported largely in the form of HCO_3^-. A small amount is transported in the dissolved form and some is carried in the form of carbaminohemoglobin. The bottom left panel shows that the CO_2 equilibrium (dissociation) curve is much steeper than that for O_2, which is why the Pco_2 difference between arterial and mixed venous blood is small (about 5 mm Hg).

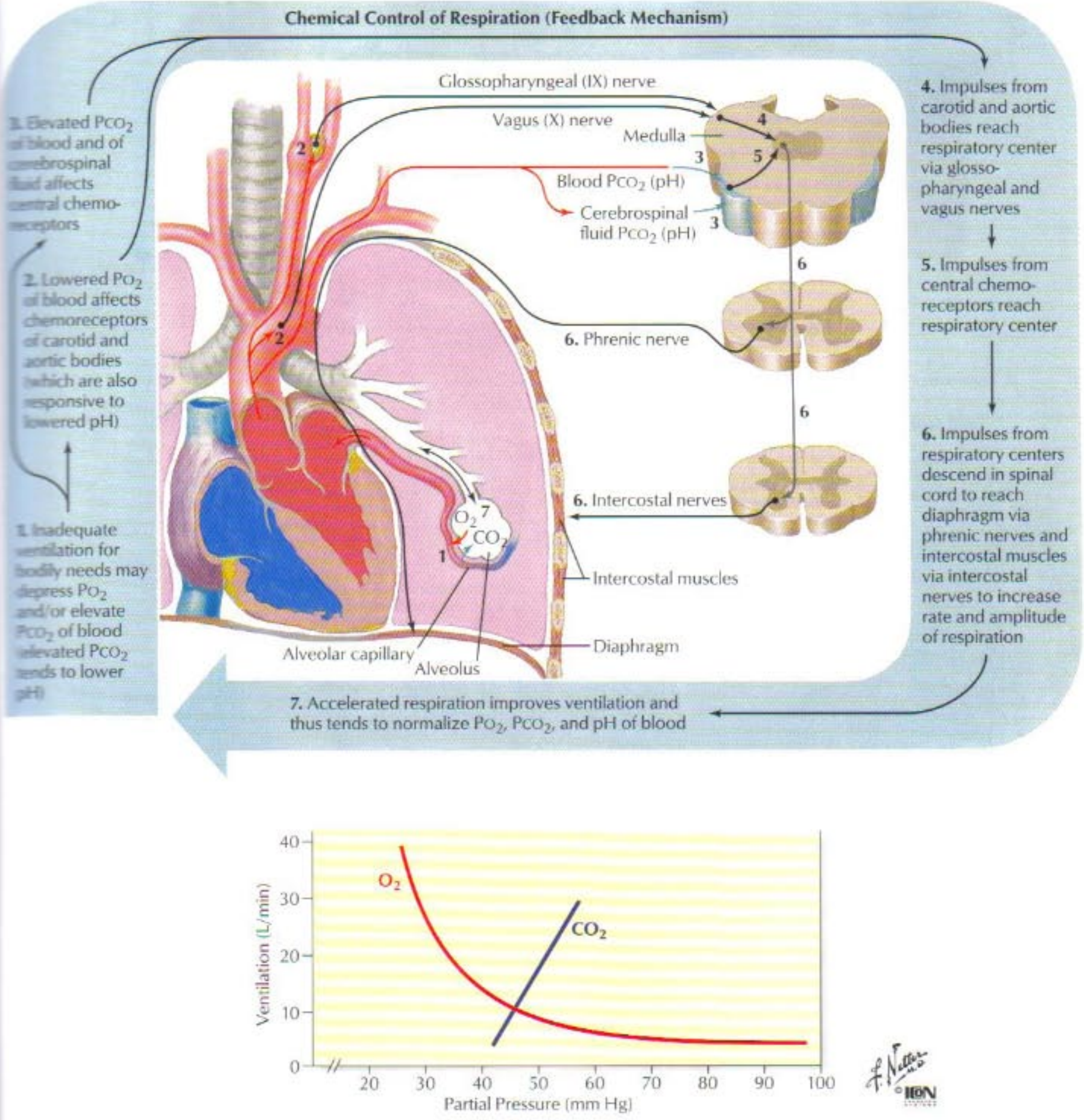
Chemical Control of Respiration (Feedback Mechanism)
3. Elevated Pco2 of blood and of cerebrospinal fluid affects central chemoreceptors
2. Lowered Po2 of blood affects chemoreceptors of carotid and aortic bodies (which are also responsive to lowered pH)
1. Inadequate ventilation for bodily needs may depress Po2 and/or elevate Pco2 of blood (elevated Pco2 tends to lower pH)
Glossopharyngeal (IX) nerve
Vagus (X) nerve
Medulla
Blood Pco2 (pH)
Cerebrospinal fluid Pco2 (pH)
6. Phrenic nerve
6. Intercostal nerves
Intercostal muscles
Diaphragm
Alveolar capillary
Alveolus
O2
CO2
1
2
3
4
5
6
7
4. Impulses from carotid and aortic bodies reach respiratory center via glossopharyngeal and vagus nerves
5. Impulses from central chemoreceptors reach respiratory center
6. Impulses from respiratory centers descend in spinal cord to reach diaphragm via phrenic nerves and intercostal muscles via intercostal nerves to increase rate and amplitude of respiration
7. Accelerated respiration improves ventilation and thus tends to normalize Po2, Pco2, and pH of blood
Ventilation (L/min)
40
30
20
10
0
O2
CO2
20
30
40
50
60
70
80
90
100
Partial Pressure (mm Hg)
F. Netter M.D.
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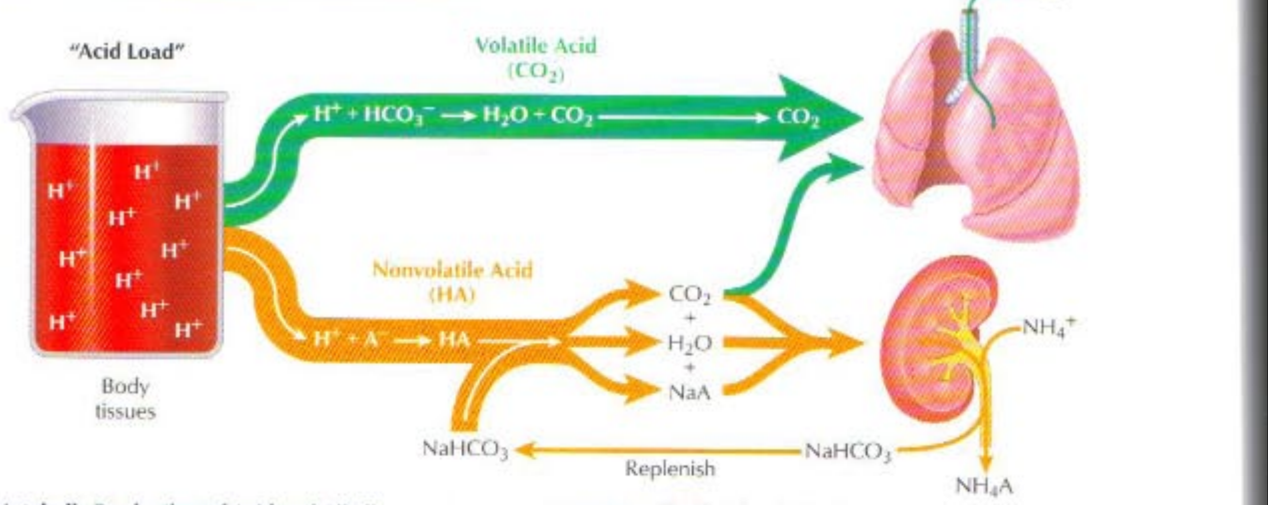
FIGURE 5.22 CONTROL OF RESPIRATION

The central chemoreceptors respond to changes in arterial P_{CO_2}, but not arterial P_{O_2} or pH. Elevated P_{CO_2} of arterial blood stimulates central brainstem chemoreceptors via changes in the pH of the cerebrospinal and brain interstitial fluid. The increased P_{CO_2} results in a decrease in pH, and this in turn increases the rate and amplitude of respiration. Peripheral chemoreceptors (carotid and aortic bodies) sense changes in the arterial blood P_{CO_2}, P_{O_2}, and pH, and send signals via the glossopharyngeal and vagus nerves to the brainstem respiratory centers. The increase in respiratory rate and amplitude seen with a decrease in arterial P_{O_2} (hypoxia) or a decrease in arterial pH is mediated by the peripheral chemoreceptors.

A. Role of Lungs and Kidneys in Acid-Base Balance

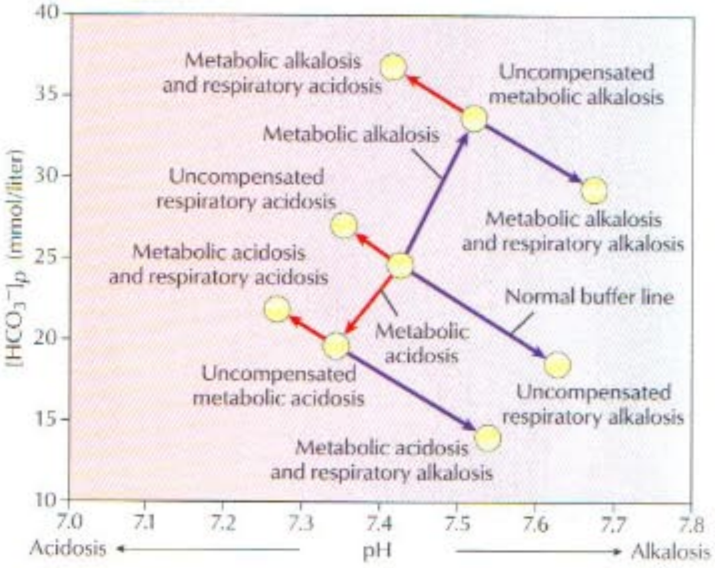


B. Metabolic Production of Acid and Alkali

Food Source	Acid/Alkali	Quantity (mEq/day)
Carbohydrate Fat	CO_2	15 - 20,000
Amino acids		
S-containing	H_2SO_4	100 (acid)
Cationic	HCl	
Anionic	HCO_3^-	
Organic ions	HCO_3^-	60 (alkali)
Phosphate	$H_2PO_4^-$	30 (acid)
Total		**70 (acid)**

1 mEq/kg/day of nonvolatile acid production

C. Acid-Base Paths



D. Acid-Base Disorders

Disorder	pH	1° Alteration	Defense Mechanisms
Metabolic acidosis	↓	↓ [HCO_3^-]	Buffers, ↓ PCO_2, ↑ NAE
Metabolic alkalosis	↑	↑ [HCO_3^-]	Buffers, ↑ PCO_2, ↓ NAE
Respiratory acidosis	↓	↑ PCO_2	Buffers & ↑ NAE
Respiratory alkalosis	↑	↓ PCO_2	Buffers & ↓ NAE

J. Perkins
MS, MFA
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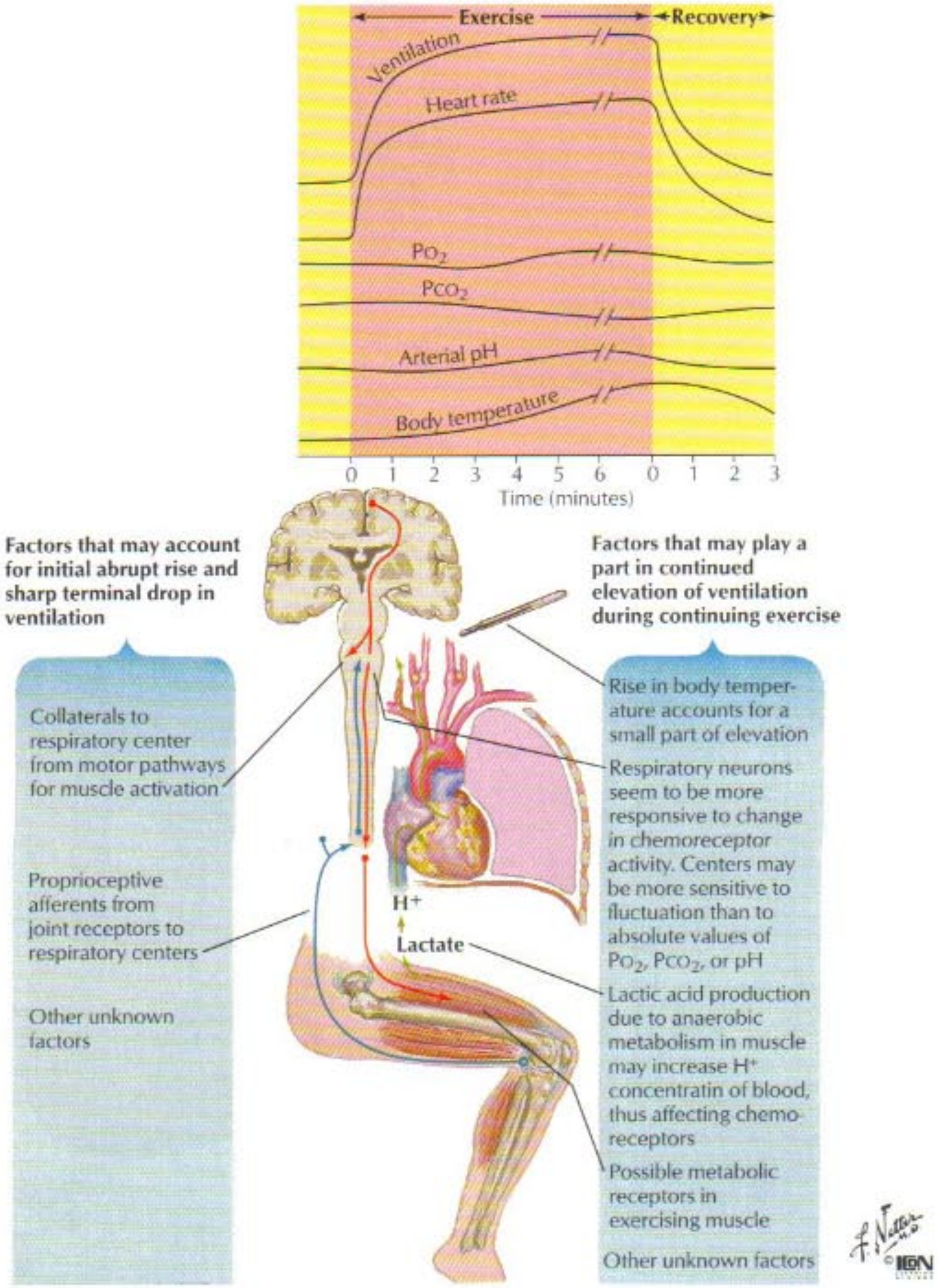
FIGURE 5.23 ACID-BASE BALANCE

A, Both the lungs and kidneys participate in acid-base balance. *B*, Our diet and cellular metabolism add acid and alkali to our system. In a typical meat-containing diet, there is the addition of acid to our body fluids. CO_2 (sometimes referred to as "volatile acid"), generated by carbohydrate and fat metabolism, is efficiently eliminated by the lungs and does not normally affect acid-base balance. However, failure to excrete the CO_2 can alter acid-base balance. Nonvolatile acid (e.g., lactic acid) is buffered by HCO_3^- in the extracellular fluid. The kidneys must excrete this nonvolatile acid and replenish the HCO_3^- used to neutralize these acids. The kidneys do this by excreting the acid anion with NH_4^+ (the kidneys also excrete H^+, which also results in the addition HCO_3^- to the extracellular fluid (see Figure 6.18). The lungs serve as a respiratory "buffer" that can respond quickly and remove large quantities of volatile acid (CO hyperventilation. The kidneys take hours or days to respond to an acid-base imbalance and do so largely by varying the amount of NH_4^+ excreted in the urine. *C* and *D* illustrate acid-base disorders resulting from alterations in the P_{CO_2} (respiratory disorders) or alterations in the [HCO_3^-] (metabolic disorders). When an acid-base disturbance occurs, intracellular (primarily proteins) and extracellular (primarily HCO_3^-) buffers minimize the change in body fluid pH. In addition, the lungs can adjust the P_{CO_2} to compensate for metabolic disorders, and the kidneys can adjust net acid excretion to compensate for respiratory disorders. *Note:* Net acid excretion (NAE) includes acid excreted with urinary buffers and as NH_4^+, less any HCO_3^- lost in the urine.



Factors that may account for initial abrupt rise and sharp terminal drop in ventilation

Collaterals to respiratory center from motor pathways for muscle activation

Proprioceptive afferents from joint receptors to respiratory centers

Other unknown factors

Factors that may play a part in continued elevation of ventilation during continuing exercise

Rise in body temperature accounts for a small part of elevation

Respiratory neurons seem to be more responsive to change in chemoreceptor activity. Centers may be more sensitive to fluctuation than to absolute values of P_{O_2}, P_{CO_2}, or pH

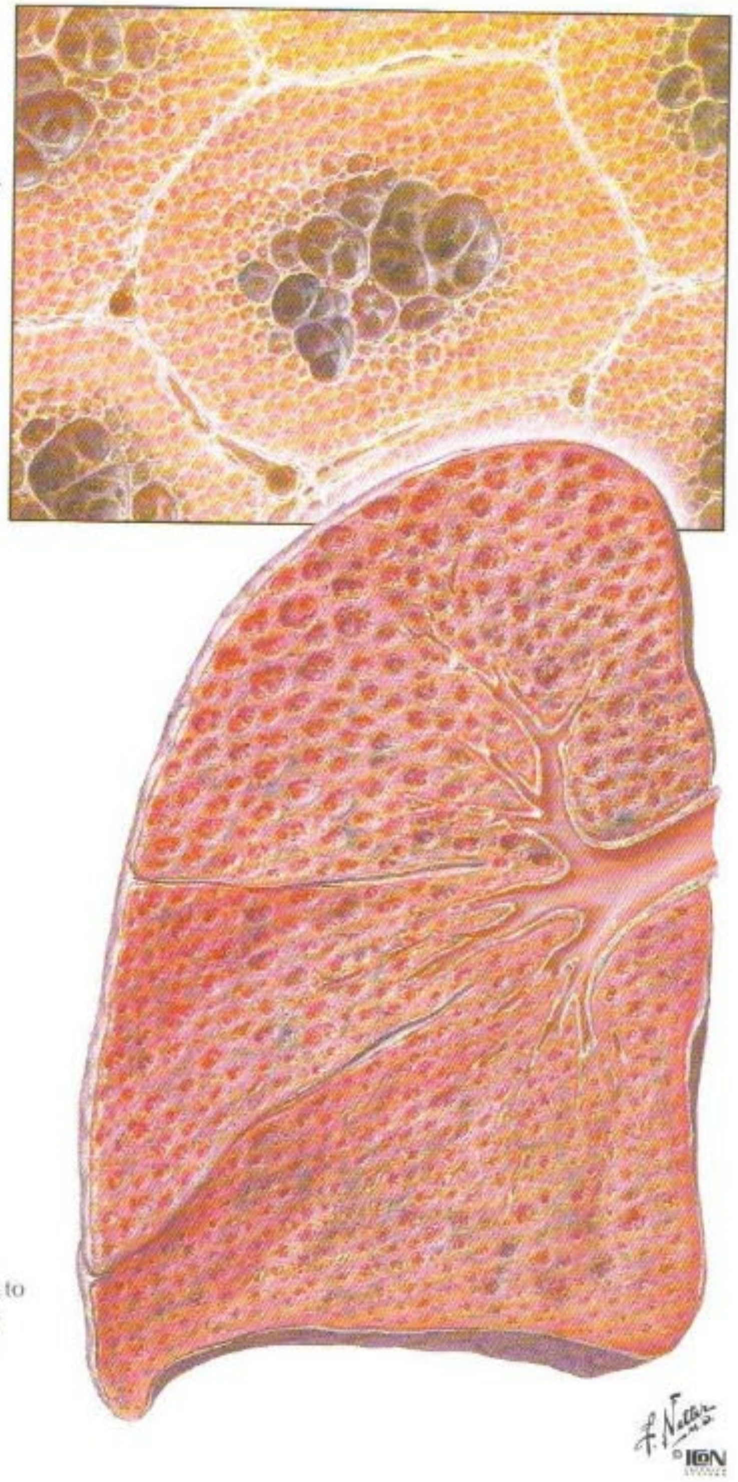
Lactic acid production due to anaerobic metabolism in muscle may increase H^+ concentratin of blood, thus affecting chemoreceptors

Possible metabolic receptors in exercising muscle

Other unknown factors

FIGURE 5.24 RESPIRATORY RESPONSE TO EXERCISE

Exercise increases the demand for delivery of O_2 to the tissues and the excretion of CO_2, both of which require an increase in the ventilatory rate. The ventilatory rate increases concurrently with the exercise-induced increase in cardiac output (represented here as an increase in heart rate). A number of factors are involved in this response and are indicated.



Centriacinar (Centrilobular) Emphysema

Magnified section. Distended, intercommunicating, saclike spaces in central area of acini

Gross specimen. Involvement tends to be most marked in upper part of lung

FIGURE 5.25 OBSTRUCTIVE DISEASE: EMPHYSEMA

This figure shows the gross and microscopic appearance of a lung as it appears in a person with centriacinar (centrolobular) emphysema. Note the dilated air spaces and rupture of the alveolar walls.

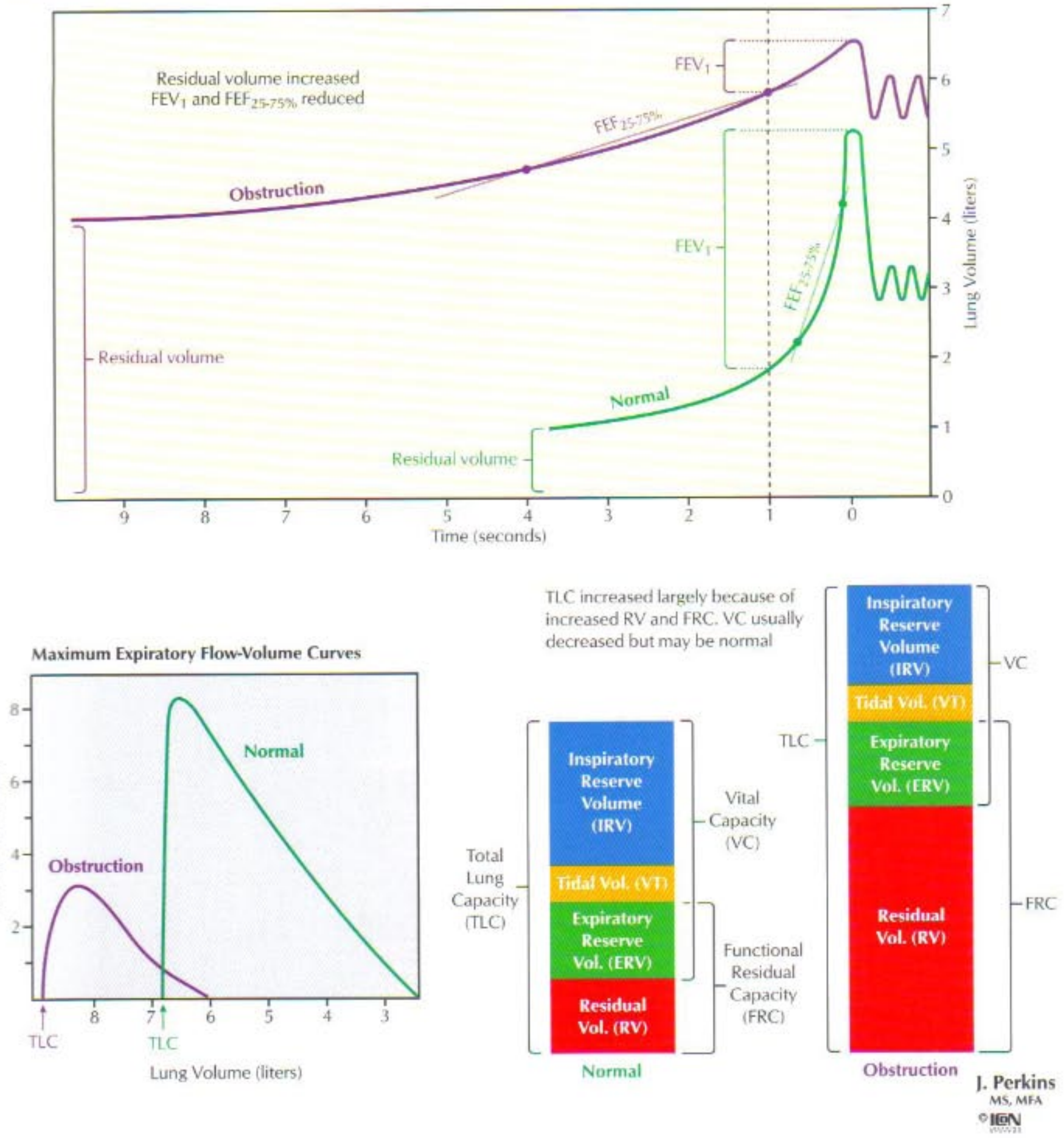


Figure 5.26 Obstructive Lung Disease

Obstructive pulmonary disease refers to a group of conditions (e.g., emphysema, chronic bronchitis, and asthma), all of which cause shortness of breath and obstruction of airflow. Shown here is the effect of severe emphysema on pulmonary function. In emphysema, inflammatory processes destroy the connective tissue of the lung, and in particular the elastic fibers that help maintain the patency of the airways (i.e., elastic recoil). Therefore, lung compliance is increased. The decreased elastic recoil results in collapse of airways during expiration (a process termed dynamic compression; see Figure 5.12) and air trapping. The trapped air results in an increase in TLC and FRC as a result of a large increase in RV. In addition, dynamic compression of the airway prolongs the forced expiratory volume in the first second (FEV$_1$), as well as the force expiratory flow rate measured over the middle half of expiration (FEF$_{25-75\%}$). Because the VC (measured as forced vital capacity [FVC]) is only slightly decreased, or even normal, the ratio of FEV$_1$/FVC is typically less than 75%.

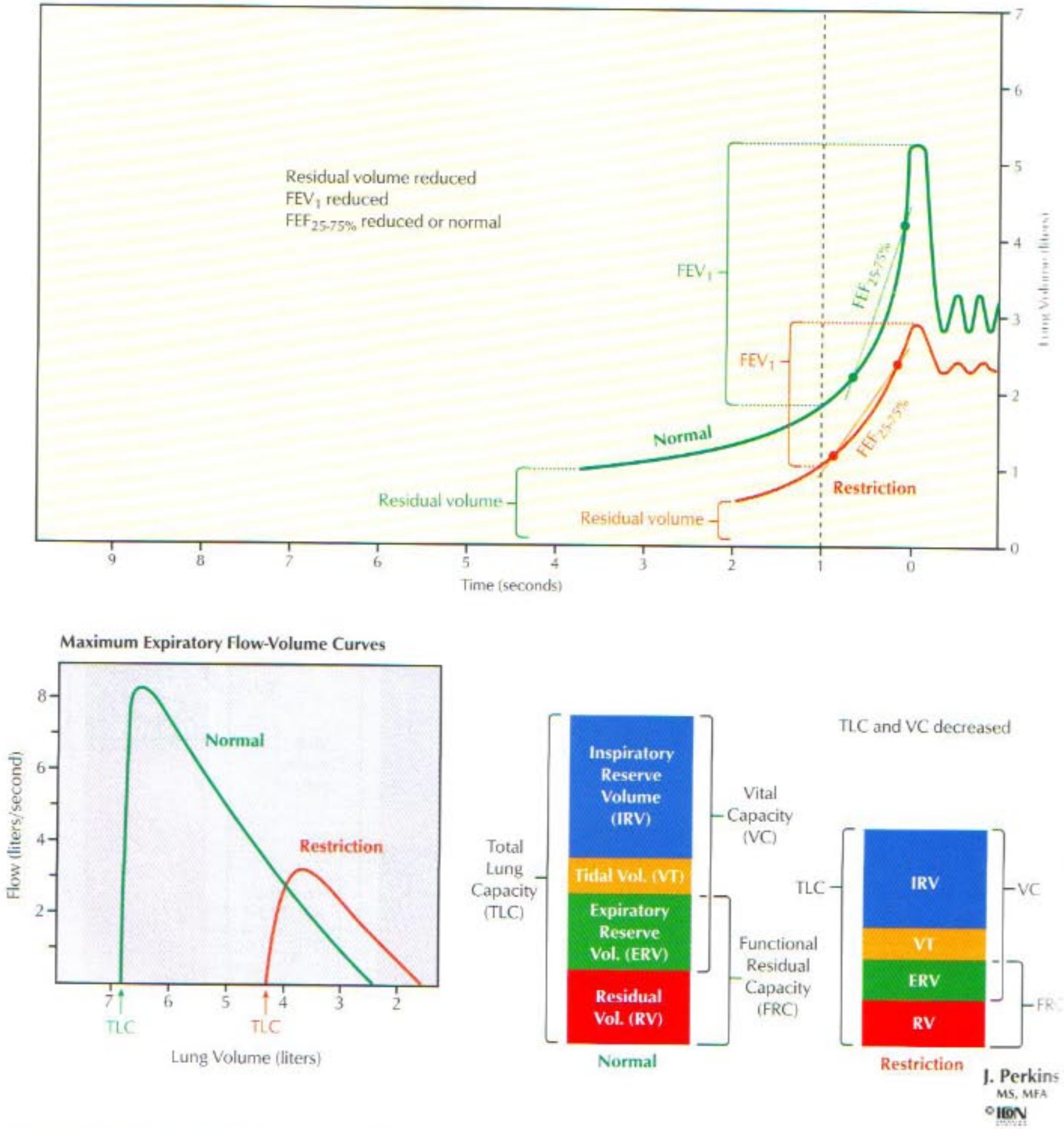
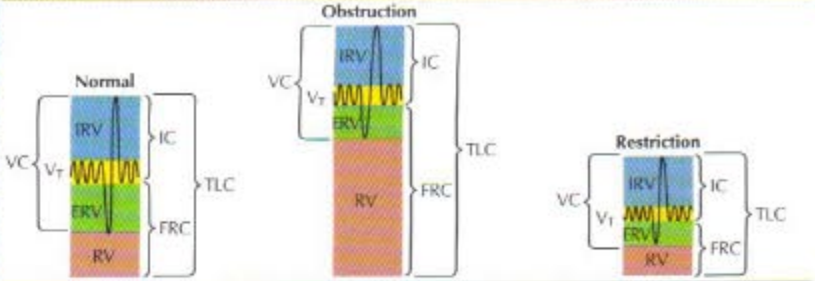
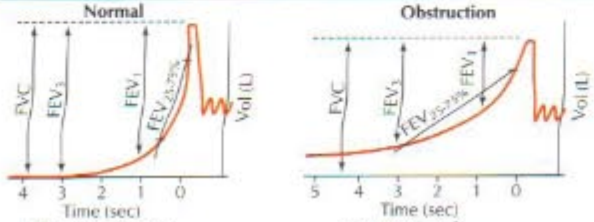
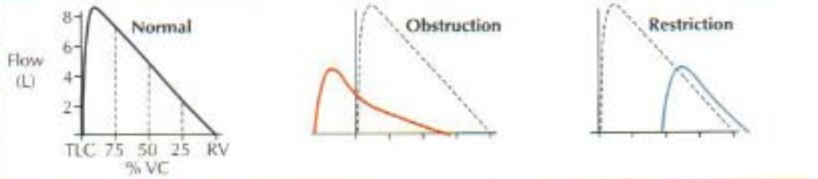
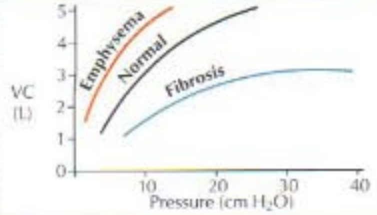
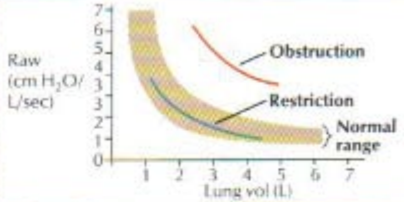


Figure 5.27 Restrictive Pulmonary Disease

Restrictive pulmonary disease refers to a group of disorders that result in an increase in the connective tissue of the lung (e.g., fibrosis, alveolar wall thickening). The increased connective tissue reduces lung compliance, making it increasingly difficult to expand the lung during inspiration. As a result, virtually all lung volumes are reduced. In particular, as shown here, there can be marked decreases in TLC and VC (measured as forced vital capacity [FVC]). The forced expiratory volume in the first second (FEV_1) is decreased in proportion to FVC, so the ratio of FEV_1/FVC is typically normal. If the FVC is markedly decreased, this ratio may even increase.

Test	Symbol	Method	Interpretation
Lung volumes and capacities			
Vital capacity	VC	Spirometer	
Inspiratory capacity	IC	Spirometer	
Expiratory reserve volume	ERV	Spirometer	
Tidal volume	V_T	Spirometer	
Functional residual capacity	FRC	He dilution or body plethysmograph	
Residual volume	RV	FRC − ERV	
Total lung capacity	TLC	VC + RV or FRC + IC	
Expiratory flow rates			 Normal: FEV_1/FVC, % > 70 FEV_3/FVC, % >95 $FEF_{25-75\%}$: wide range Obstruction: FEV_1/FVC, % FEV_3/FVC, % $FEF_{25-75\%}$ Decreased **Restriction** FEV_1/FVC, % and FEV_3/FVC, % usually normal $FEF_{25-75\%}$ reduced or normal
Forced expiratory volume in 1 second *in 3 seconds*	FEV_1 FEV_3	Spirometer	
Forced mid-expiratory flow	$FEV_{25-75\%}$ (FMF)	Spirometer	
Maximal expiratory flow-volume curve	MEFV	Spirometer with simultaneous recording of flow and volume and volume of integrated pneumotachograph	
Maximal expiratory flow at 75, 50, 25 % of VC	$\dot{V}_{max\,75}$ $\dot{V}_{max\,50}$ $\dot{V}_{max\,25}$		
Lung elasticity		Pleural pressure is recorded with esophageal balloon while airflow is arrested at different lung volumes; changes in lung volume recorded with spirometer or pneumotachograph	 Static elastic recoil of lung is increased and static compliance reduced in diseases such as pulmonary fibrosis. Conversely, in emphysema, static lung compliance is increased and elastic recoil is reduced
Static recoil pressure	P_{stat}		
Static compliance	C_{stat}		
Airway resistance	Raw	Body plethysmograph to determine alveolar pressure and pneumotachograph to measure airflow	 In obstructive lung disease airway resistance is increased. If obstruction involves only small airways (<2 mm diameter), only minimal changes in overall resistance may result. In restrictive disorders, resistance is often reduced because of increased traction on intrathoracic airway walls
Diffusing capacity	Dco	Low concentration of CO inhaled; expired gas analyzed for CO	Diffusing capacity is reduced when alveolar walls are destroyed and pulmonary capillaries are obliterated by emphysema and when alveolar-capillary membrane is thickened by edema, consolidation, or fibrosis

Obstruction
Normal
Restriction
IRV
IC
VC
V_T
ERV
TLC
FRC
RV

Normal
Obstruction
FVC
FEV_3
FEV_1
$FEV_{25-75\%}$
Vol (L)
4 3 2 1 0
5 4 3 2 1 0
Time (sec)

Normal
Obstruction
Restriction
Flow (L)
8
6
4
2
TLC 75 50 25 RV
% VC

Emphysema
Normal
Fibrosis
VC (L)
5
4
3
2
1
0
10 20 30 40
Pressure (cm H_2O)

Raw (cm H_2O/ L/sec)
7 6 5 4 3 3 2 1 0
Obstruction
Restriction
Normal range
1 2 3 4 5 6 7
Lung vol (L)

F. Netter M.D. © ICON

FIGURE 5.28 TESTS OF PULMONARY FUNCTION

This figure illustrates pulmonary function tests and comparative values for normal lungs and diseased lungs (obstructive or restrictive disease).

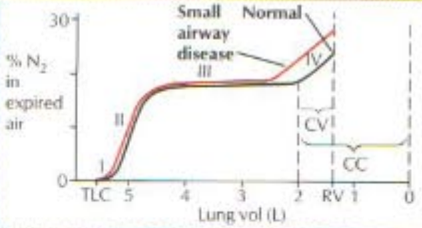
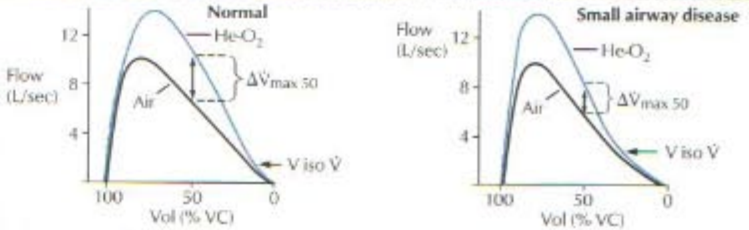
Test	Symbol	Method	Interpretation	
Tests for small airway disease Closing volume Closing capacity	CV CC	Following a full inspiration of O_2 the expired lung volume from TLC to RV is plotted against the N_2 concentration		Airways in the lower lung zones close at low lung volumes and only those alveoli at top of lungs continue to empty. Because concentration of N_2 in alveoli of upper zones is higher, the slope of the curve abruptly increases (phase IV). Phase IV begins at larger lung volumes in individuals with even minor degrees of airway obstruction increasing both CV and CC
Maximal expiratory flow-volume curve breathing 80% He and 20% O_2	$\Delta\dot{V}_{max\,50}$ $V\ iso\ \dot{V}$	Spirometer or pneumotachograph to record flow and volume	 During a maximal expiratory maneuver, resistance to airflow is normally due to turbulence and convective acceleration. Breathing He, which is less dense than air, lowers resistance and increases flow at all but the lowest volumes. In small airway disease, resistance to laminar flow makes up larger portion of total resistance and airflow is relatively independent of gas density. Increase in expiratory flow at 50% of VC while breathing He-O_2 ($\Delta\dot{V}_{max\,50}$) will be less, and volume at which flows while breathing He-O_2 and while breathing air are identical ($V\ iso\ \dot{V}$) will be higher in patients with small airway disease than in normal individuals	
Gas exchange			**Normal values**	**Abnormalities**
Partial pressure of O_2 in arterial blood	P_{O_2}	Arterial blood is collected anaerobically in heparinized syringe	60 to 100 mm Hg breathing room air at sea level; falls slightly with age	Hypoxemia indicative of ventilation/perfusion abnormalities, shunts, diffusion defect, alveolar hypoventilation
Partial pressure of CO_2 in arterial blood	P_{CO_2}		36 to 44 mm Hg	P_{CO_2} proportional to metabolic rate (CO_2 production) and inversely related to volume of alveolar ventilation
Arterial blood pH	pH		7.35 to 7.45 pH	Acidosis (pH <7.35) Respiratory (inadequate alveolar ventilation) Metabolic (gain of acid and/or loss of base) Alkalosis (pH >7.45) Respiratory (excessive alveolar ventilation) Metabolic (gain of base or loss of acid)
Alveolar-arterial O_2 difference	A-aD_{O_2} A-aP_{O_2}		<10 mm Hg breathing room air	Primarily reflects mismatching of ventilation and perfusion and/or shunts; may also be affected by diffusion defects
Dead space/tidal volume ratio	V_D/V_T	Determined from arterial and mixed expired P_{CO_2}	<0.3	Elevated ratio indicates wasted ventilation; i.e., that volume of gas which does not take part in gas exchange
Shunt fraction	$\dot{Q}_S/\dot{Q}_T$	Determined from P_{O_2} after a period of breathing 100% O_2	<5%	Elevation indicates increased amount of mixed venous blood entering systemic circulation without coming into contact with alveolar air, either because of shunting of blood past lungs to left side of heart or perfusion of regions of lung which are not ventilated

FIGURE 5.28 TESTS OF PULMONARY FUNCTION—CONT'D

This figure illustrates pulmonary function tests and comparative values for normal lungs and diseased lungs (obstructive or restrictive disease).

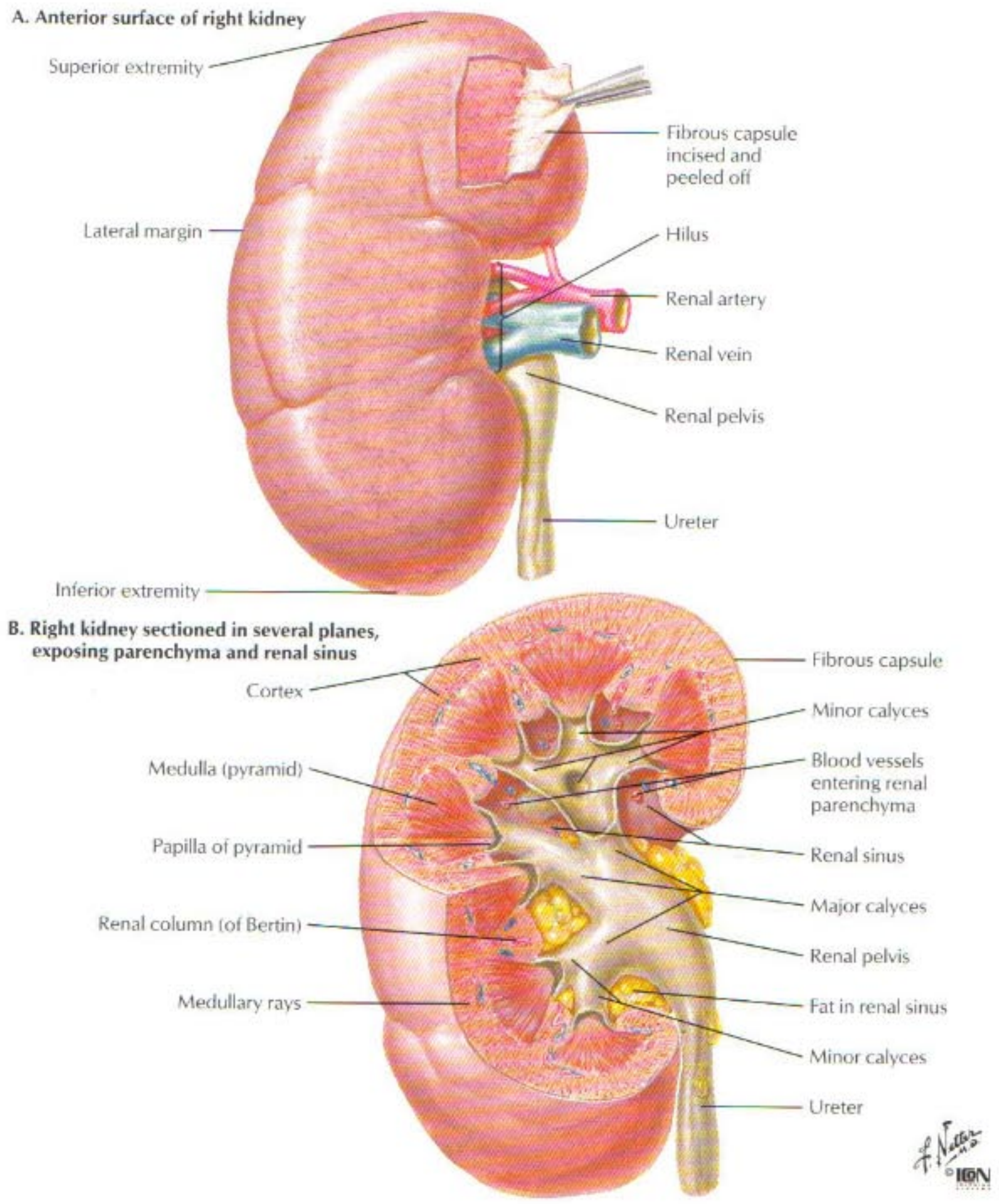

A. Anterior surface of right kidney
Superior extremity
Fibrous capsule incised and peeled off
Lateral margin
Hilus
Renal artery
Renal vein
Renal pelvis
Ureter
Inferior extremity
B. Right kidney sectioned in several planes, exposing parenchyma and renal sinus
Cortex
Fibrous capsule
Minor calyces
Medulla (pyramid)
Blood vessels entering renal parenchyma
Papilla of pyramid
Renal sinus
Major calyces
Renal column (of Bertin)
Renal pelvis
Medullary rays
Fat in renal sinus
Minor calyces
Ureter

FIGURE 6.1 ANATOMY OF THE KIDNEY

The kidneys are paired retroperitoneal abdominal organs at the level of the T11 to L3 vertebrae. They process the blood and participate in the following general functions: (1) regulating fluid volume and composition, (2) excreting metabolic wastes and removing foreign chemicals (e.g., drugs) and their metabolites from the blood, and (3) functioning as endocrine organs. Internally, the kidney is divided into a cortex and medulla, both of which contain the nephrons (approximately 1.25 million per kidney). The medulla forms 8 to 15 pyramids. Urine exits the papilla of a pyramid and collects in a minor calyx. The minor calyces join to form the major calyces and then the pelvis. The renal columns (of Bertin) consist of cortical nephron segments, whereas the medullary rays contain nephron segments that extend into the medulla.

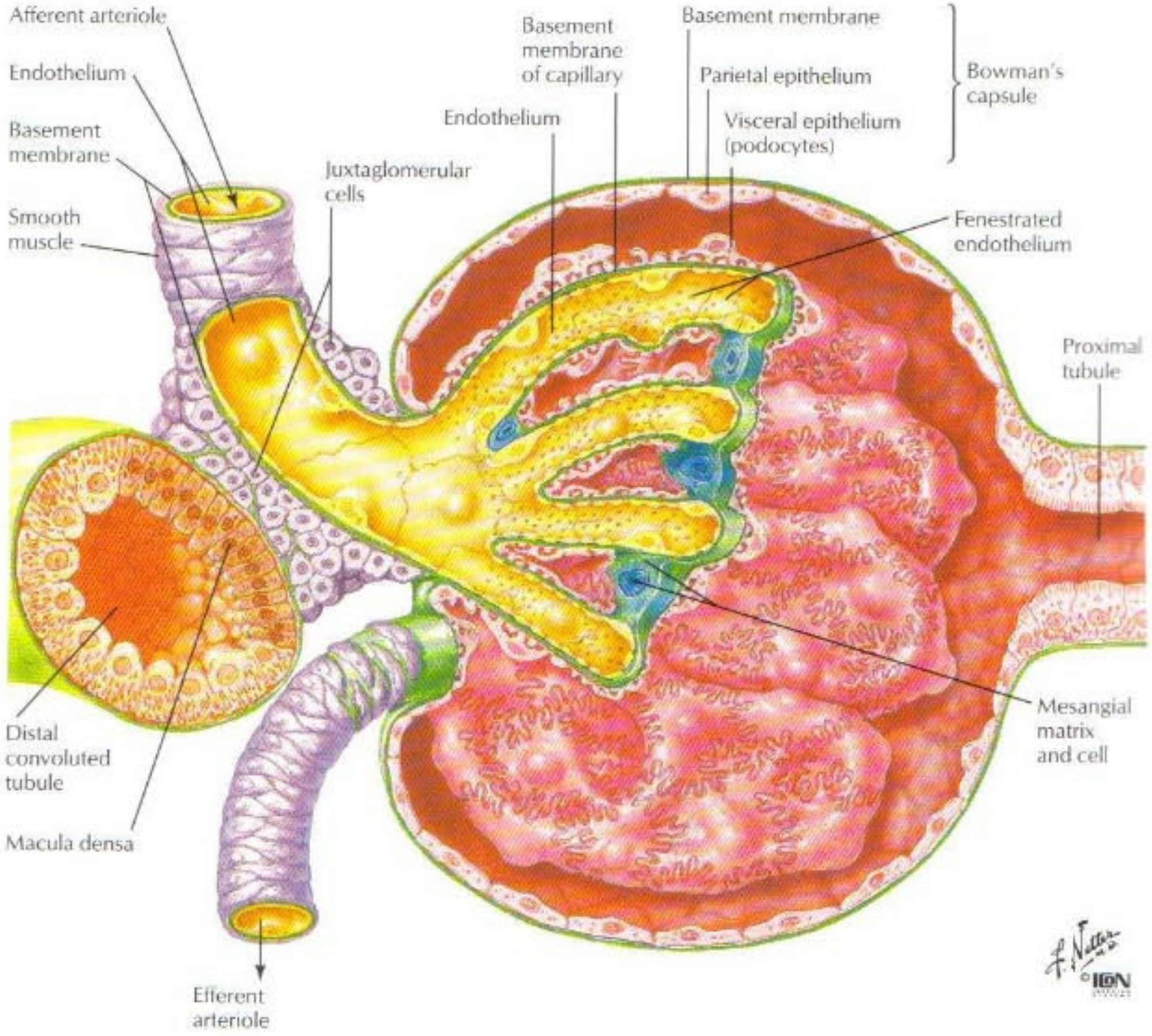
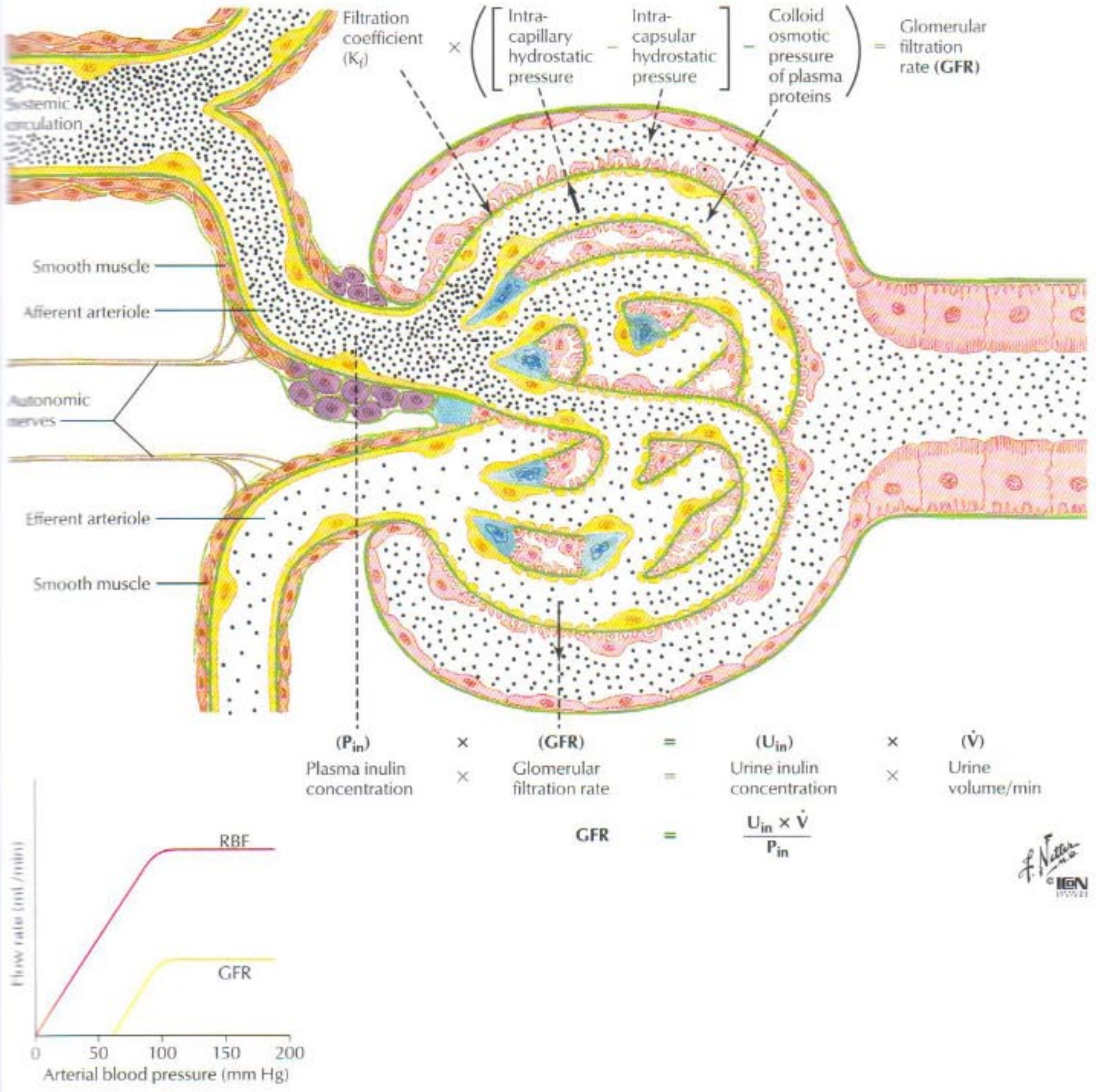

Afferent arteriole
Endothelium
Basement membrane
Smooth muscle
Juxtaglomerular cells
Endothelium
Basement membrane of capillary
Basement membrane
Parietal epithelium
Visceral epithelium (podocytes)
Bowman's capsule
Fenestrated endothelium
Proximal tubule
Mesangial matrix and cell
Distal convoluted tubule
Macula densa
Efferent arteriole
F. Netter
©ICON

FIGURE 6.3 ANATOMY OF THE GLOMERULUS

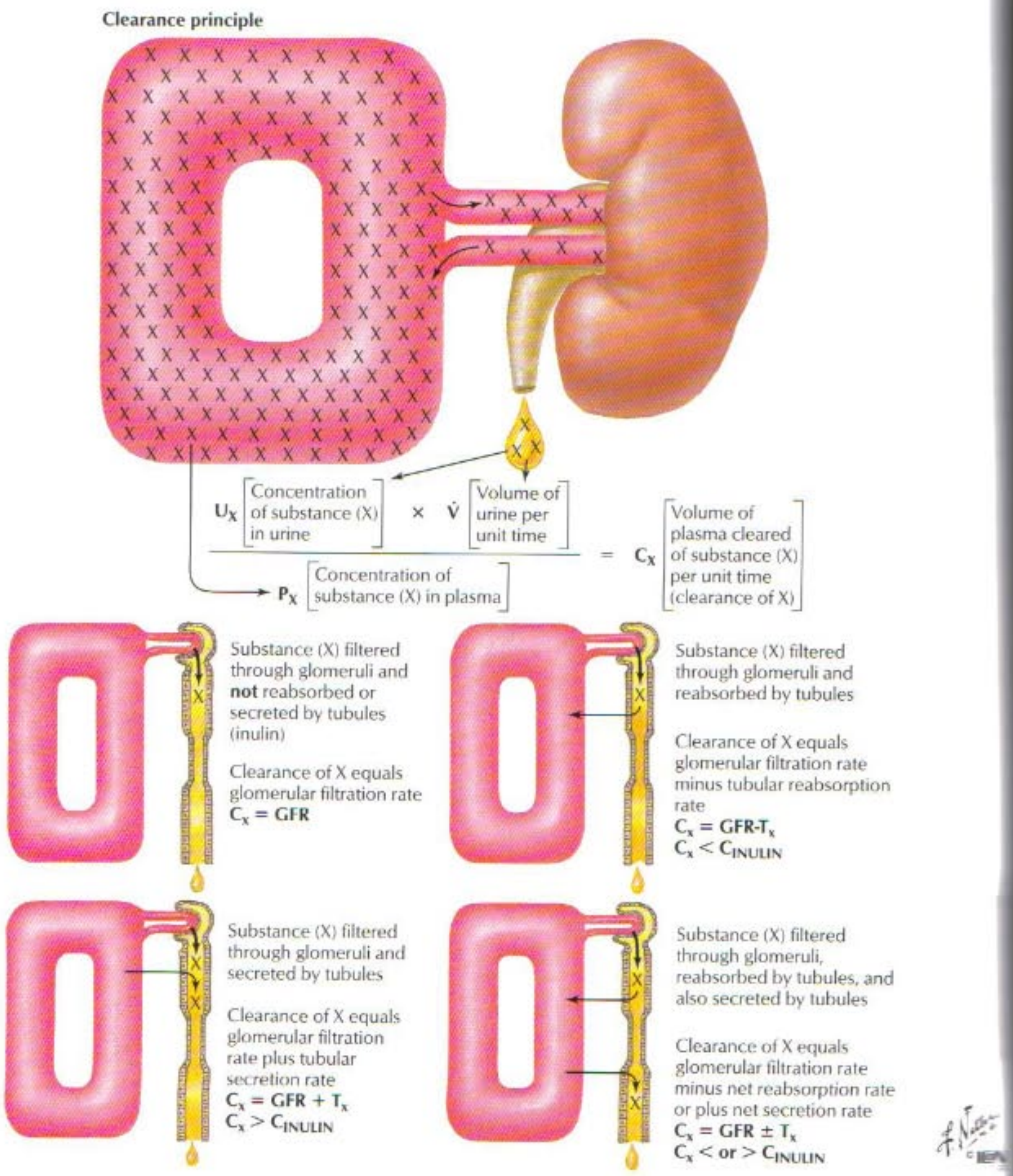
Plasma is filtered at the glomerulus. The filtrate is devoid of cells and virtually all proteins (*note:* proteins and peptides that are smaller in size than albumin are filtered to varying degrees). The endothelium of the glomerulus is fenestrated and serves to prevent the filtration of the cellular elements of blood. The basement membrane and visceral epithelial cells (podocytes) prevent the filtration of plasma proteins. The macula densa monitors the delivery of NaCl to the distal tubule and in this way helps regulate renal plasma flow and the glomerular filtration rate—a process called autoregulation.


Filtration coefficient (K_f)
×
Intra-capillary hydrostatic pressure
−
Intra-capsular hydrostatic pressure
−
Colloid osmotic pressure of plasma proteins
=
Glomerular filtration rate (GFR)
Systemic circulation
Smooth muscle
Afferent arteriole
Autonomic nerves
Efferent arteriole
Smooth muscle
(P_{in}) × (GFR) = (U_{in}) × ($\dot{V}$)
Plasma inulin concentration × Glomerular filtration rate = Urine inulin concentration × Urine volume/min
RBF
GFR
Flow rate (ml/min)
0
50
100
150
200
Arterial blood pressure (mm Hg)
F. Netter
© ICON

$$\text{GFR} = \frac{U_{in} \times \dot{V}}{P_{in}}$$

FIGURE 6.4 GLOMERULAR FILTRATION

An ultrafiltrate of plasma is produced at the glomerulus. It is devoid of cells and virtually all protein. Small molecules and ions are present at concentrations similar to those of plasma. The glomerular filtration rate (GFR) is determined by the surface area and permeability of the glomerulus (K_f) and the Starling forces across the capillary wall. Intracapillary hydrostatic pressure promotes filtration, whereas intracapsular hydrostatic pressure and capillary colloid osmotic (oncotic) pressure generated by the plasma proteins oppose filtration. The GFR is relatively constant, despite variations in blood pressure (i.e., autoregulation). Changes in intracapillary hydrostatic pressure are responsible for physiologic regulation of the GFR. When activated, sympathetic nerves constrict the afferent and efferent arterioles, reducing intracapillary hydrostatic pressure and thus the GFR. Although not shown, increased delivery of NaCl to the macula densa decreases the GFR, whereas decreased delivery increases the GFR. A number of hormones can also alter the GFR. Angiotensin II, especially at high concentrations, constricts the afferent arteriole and reduces the GFR. Atrial natriuretic peptide and prostaglandin E_2 dilate the afferent arteriole and increase the GFR. The GFR can be measured with inulin.

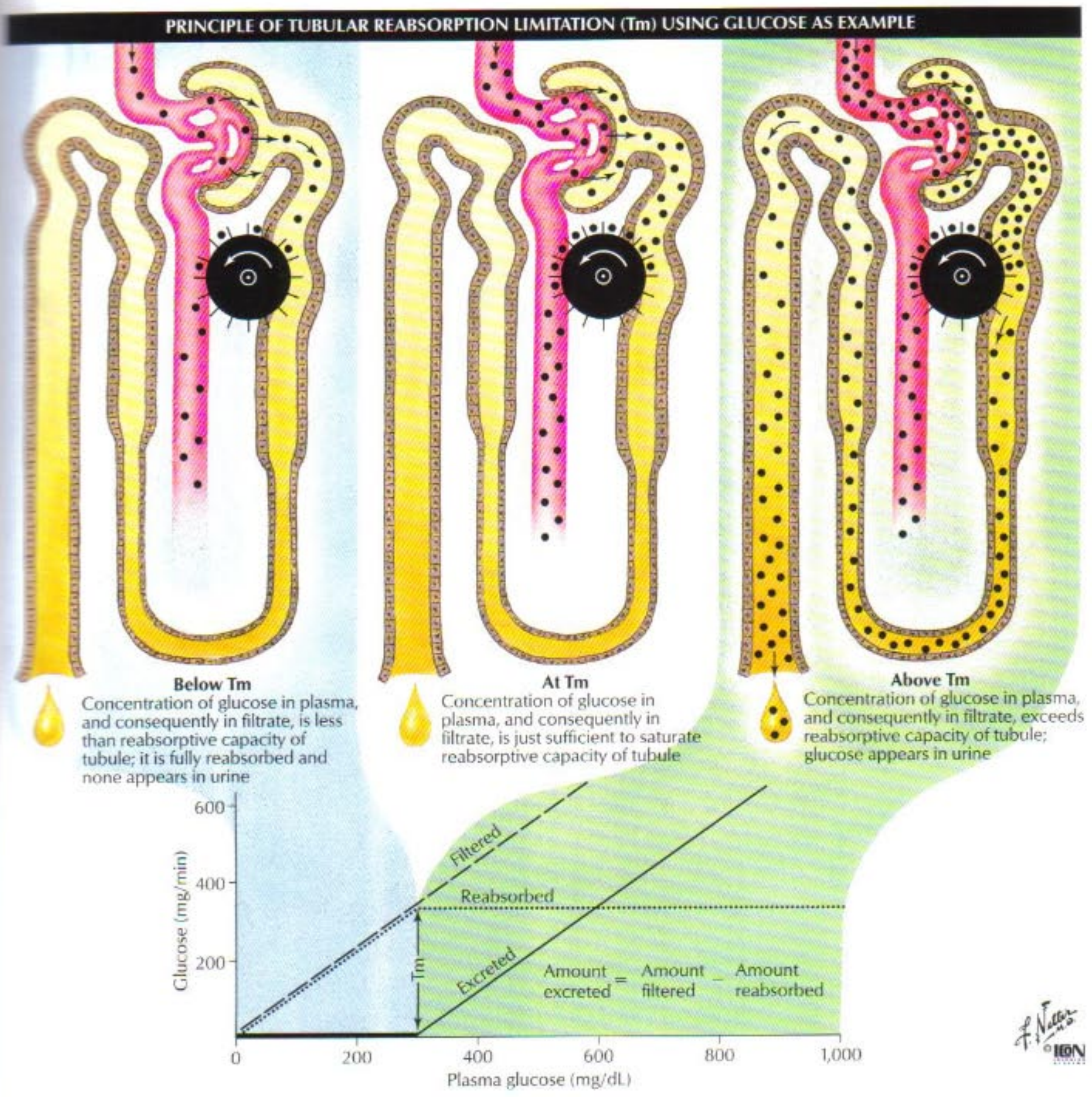


Clearance principle

X
U_X [Concentration of substance (X) in urine] × $\dot{V}$ [Volume of urine per unit time]
P_X [Concentration of substance (X) in plasma]
= C_X [Volume of plasma cleared of substance (X) per unit time (clearance of X)]
Substance (X) filtered through glomeruli and **not** reabsorbed or secreted by tubules (inulin)
Clearance of X equals glomerular filtration rate
C_x = GFR
Substance (X) filtered through glomeruli and reabsorbed by tubules
Clearance of X equals glomerular filtration rate minus tubular reabsorption rate
C_x = GFR-T_x
$C_x < C_{INULIN}$
Substance (X) filtered through glomeruli and secreted by tubules
Clearance of X equals glomerular filtration rate plus tubular secretion rate
C_x = GFR + T_x
$C_x > C_{INULIN}$
Substance (X) filtered through glomeruli, reabsorbed by tubules, and also secreted by tubules
Clearance of X equals glomerular filtration rate minus net reabsorption rate or plus net secretion rate
C_x = GFR ± T_x
C_x < or > C_{INULIN}

FIGURE 6.5 RENAL CLEARANCE

The renal clearance of a substance provides information on how that substance is handled by the kidney. The clearance of inulin provides a measure of the GFR. If a substance is freely filtered at the glomerulus and its clearance is less than that of inulin, the substance is reabsorbed by the nephron. Conversely, if the clearance is greater than that of inulin, then the substance is secreted by the nephron. Figures 6.6 and 6.7 illustrate in greater detail the handling of a substance that is reabsorbed (e.g., glucose) and a substance that is secreted (e.g., *para*-amino hippurate).



PRINCIPLE OF TUBULAR REABSORPTION LIMITATION (Tm) USING GLUCOSE AS EXAMPLE

Below Tm
Concentration of glucose in plasma, and consequently in filtrate, is less than reabsorptive capacity of tubule; it is fully reabsorbed and none appears in urine

At Tm
Concentration of glucose in plasma, and consequently in filtrate, is just sufficient to saturate reabsorptive capacity of tubule

Above Tm
Concentration of glucose in plasma, and consequently in filtrate, exceeds reabsorptive capacity of tubule; glucose appears in urine

600
400
200
Glucose (mg/min)
Filtered
Reabsorbed
Excreted
Tm
Amount excreted = Amount filtered − Amount reabsorbed
0
200
400
600
800
1,000
Plasma glucose (mg/dL)

FIGURE 6.6 RENAL HANDLING OF GLUCOSE

Glucose is filtered at the glomerulus and reabsorbed by the proximal tubule. Normally, no glucose appears in the urine because all of the filtered glucose is reabsorbed. However, as the plasma concentration of glucose is increased (e.g., as can occur in diabetes mellitus), glucose appears in the urine. Therefore, the renal clearance of glucose will increase as the plasma concentration of glucose increases.

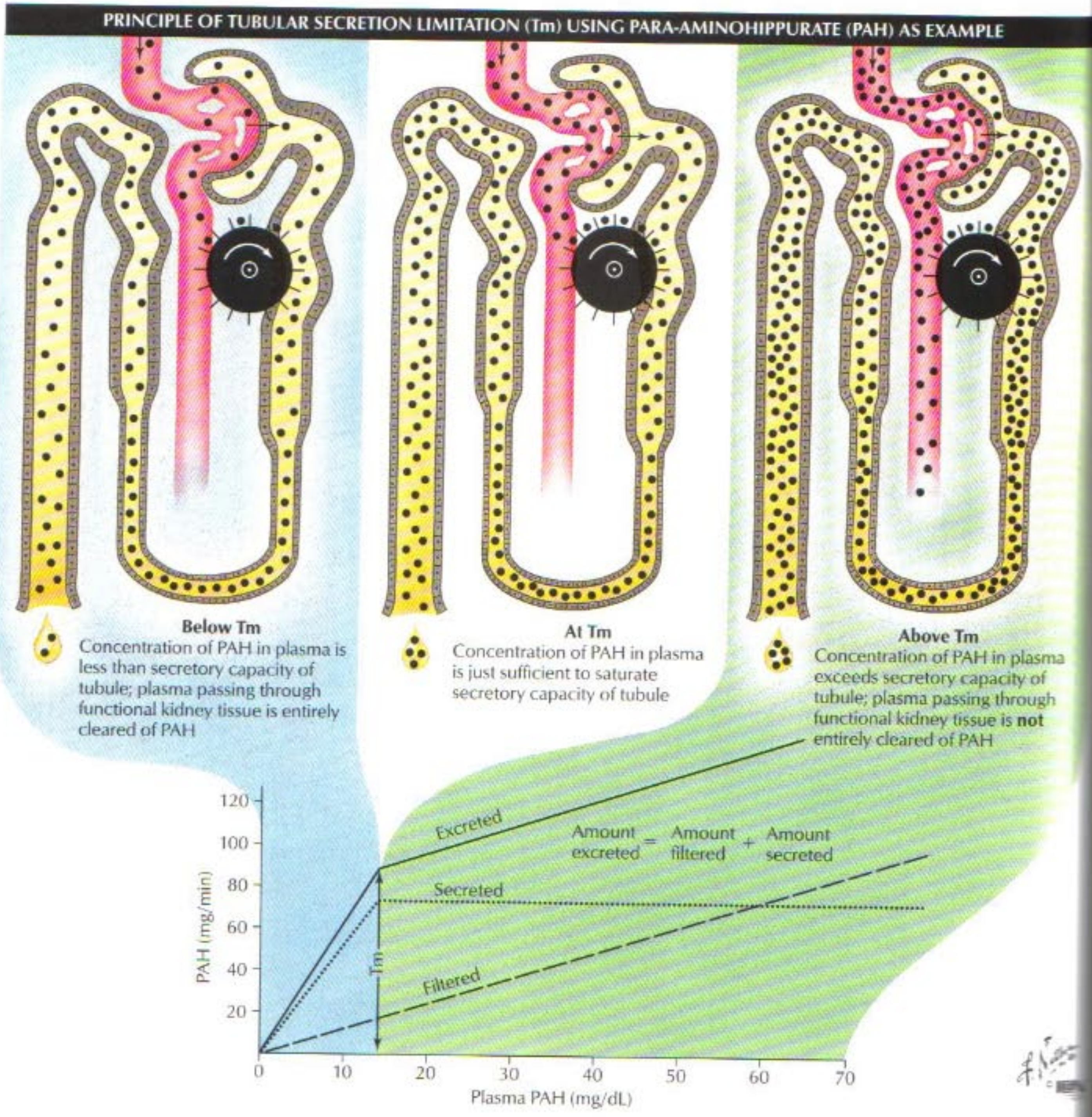
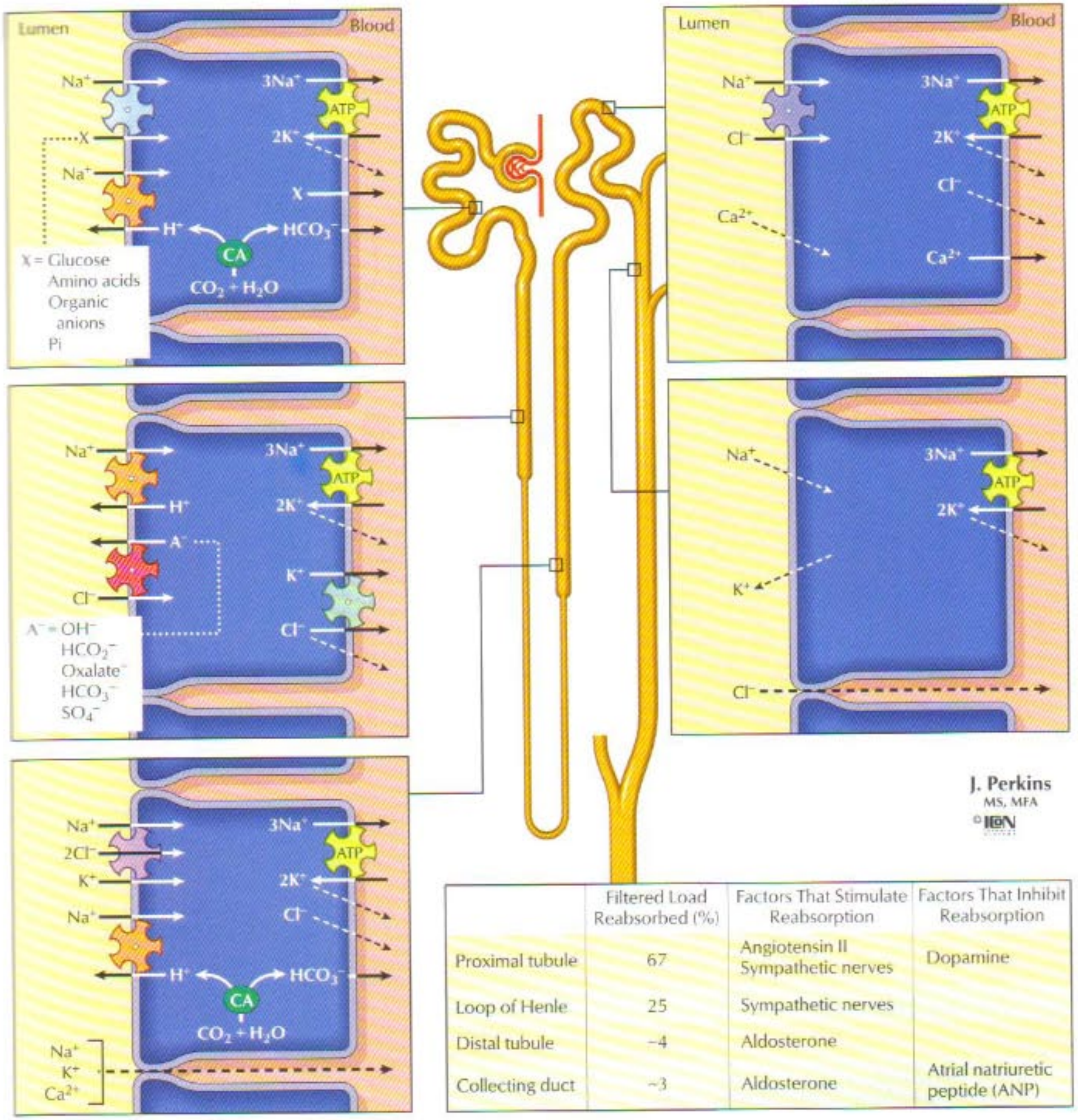

PRINCIPLE OF TUBULAR SECRETION LIMITATION (Tm) USING PARA-AMINOHIPPURATE (PAH) AS EXAMPLE
Below Tm
Concentration of PAH in plasma is less than secretory capacity of tubule; plasma passing through functional kidney tissue is entirely cleared of PAH
At Tm
Concentration of PAH in plasma is just sufficient to saturate secretory capacity of tubule
Above Tm
Concentration of PAH in plasma exceeds secretory capacity of tubule; plasma passing through functional kidney tissue is **not** entirely cleared of PAH
Excreted
Amount excreted = Amount filtered + Amount secreted
Secreted
Filtered
Tm
PAH (mg/min)
120
100
80
60
40
20
0
10
20
30
40
50
60
70
Plasma PAH (mg/dL)

Figure 6.7 Renal Handling of *para*-Amino Hippurate (PAH)

PAH is filtered at the glomerulus and secreted into the tubular fluid by the proximal tubule. At low plasma PAH concentrations, virtually all the PAH is excreted into the urine. At this point the clearance of PAH approximates the renal plasma flow. As the plasma concentration PAH is increased, the secretory capacity of the proximal tubule is exceeded and the renal clearance of PAH decreases.


Lumen
Blood
Na+
X
Na+
3Na+
ATP
2K+
X
H+
HCO3−
CA
CO2 + H2O
X = Glucose
Amino acids
Organic
anions
Pi
Na+
H+
A−
Cl−
3Na+
ATP
2K+
K+
Cl−
A− = OH−
HCO2−
Oxalate−
HCO3−
SO4−
Na+
2Cl−
K+
Na+
3Na+
ATP
2K+
Cl−
H+
HCO3−
CA
CO2 + H2O
Na+
K+
Ca2+
Lumen
Blood
Na+
Cl−
Ca2+
3Na+
ATP
2K+
Cl−
Ca2+
Na+
K+
Cl−
3Na+
ATP
2K+
J. Perkins
MS, MFA
© ICON

	Filtered Load Reabsorbed (%)	Factors That Stimulate Reabsorption	Factors That Inhibit Reabsorption
Proximal tubule	67	Angiotensin II Sympathetic nerves	Dopamine
Loop of Henle	25	Sympathetic nerves	
Distal tubule	~4	Aldosterone	
Collecting duct	~3	Aldosterone	Atrial natriuretic peptide (ANP)

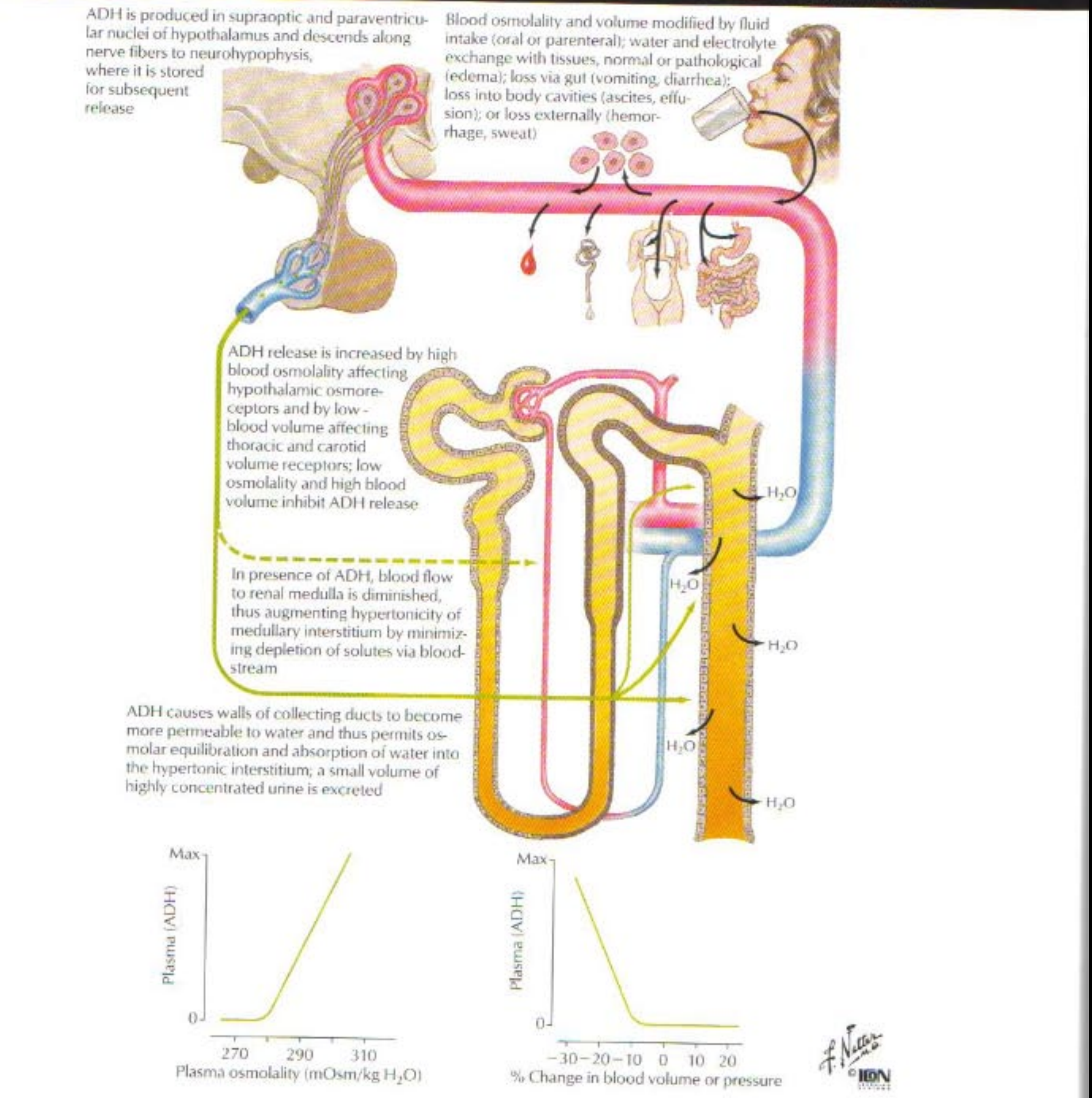
FIGURE 6.8 RENAL Na^+ REABSORPTION

A large amount of Na^+ is filtered by the glomeruli each day. This filtered load (FL) is calculated as follows:

FL = GFR × Plasma $[Na^+]$ **or**
25,200 mEq/day = 180 L/day × 140 mEq/L

Normally, 99% or more of this filtered Na^+ is reabsorbed along the nephron (i.e., only 100 to 200 mEq/day is excreted). Depicted here are the primary mechanisms for Na^+ reabsorption. Also summarized is the percent of the filtered load of Na^+ reabsorbed by each segment and some of the factors that either stimulate or inhibit reabsorption in these segments.

MECHANISM OF ANTIDIURETIC HORMONE IN REGULATING URINE VOLUME AND CONCENTRATION



ADH is produced in supraoptic and paraventricular nuclei of hypothalamus and descends along nerve fibers to neurohypophysis, where it is stored for subsequent release

Blood osmolality and volume modified by fluid intake (oral or parenteral); water and electrolyte exchange with tissues, normal or pathological (edema); loss via gut (vomiting, diarrhea); loss into body cavities (ascites, effusion); or loss externally (hemorrhage, sweat)

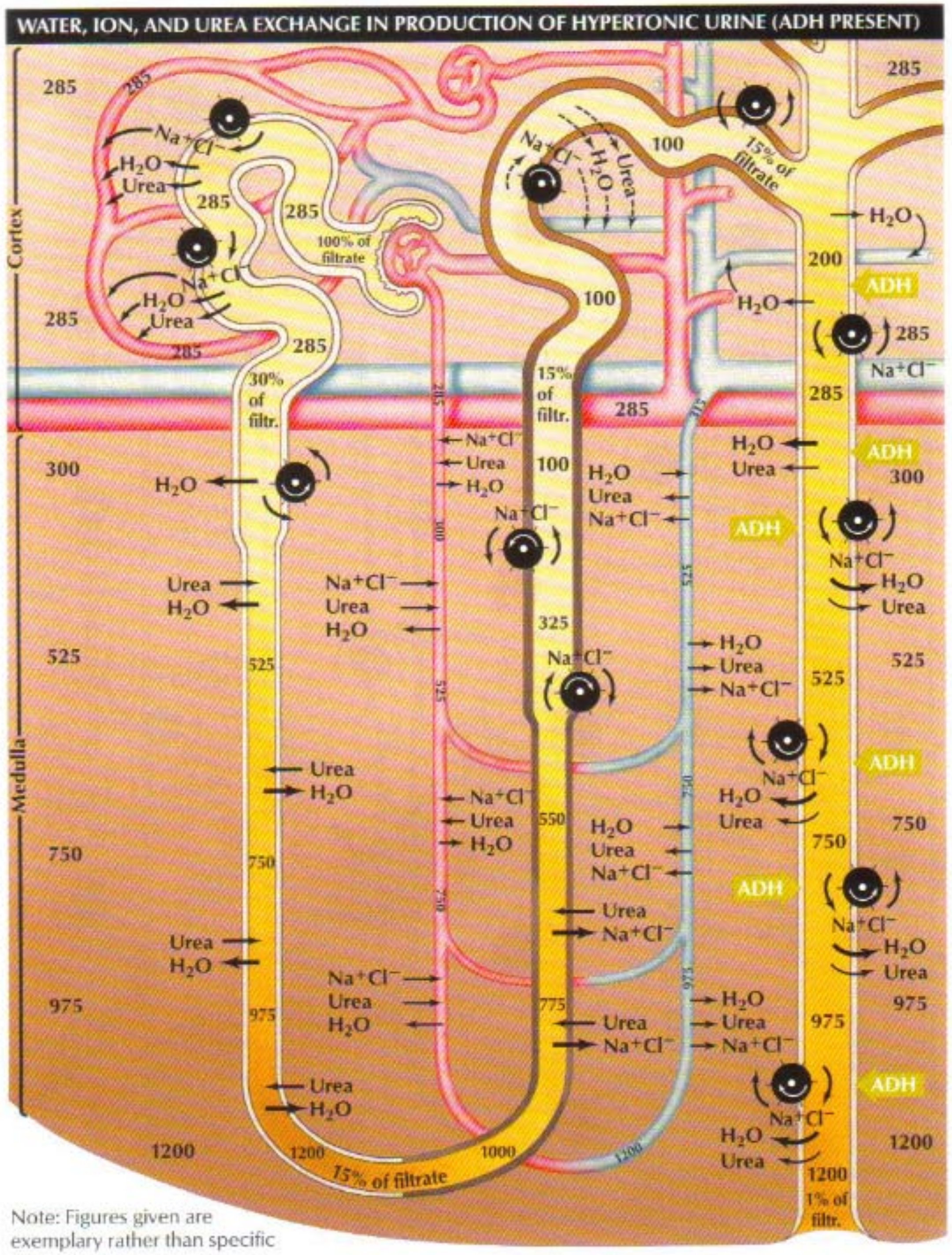
ADH release is increased by high blood osmolality affecting hypothalamic osmoreceptors and by low-blood volume affecting thoracic and carotid volume receptors; low osmolality and high blood volume inhibit ADH release

In presence of ADH, blood flow to renal medulla is diminished, thus augmenting hypertonicity of medullary interstitium by minimizing depletion of solutes via bloodstream

ADH causes walls of collecting ducts to become more permeable to water and thus permits osmolar equilibration and absorption of water into the hypertonic interstitium; a small volume of highly concentrated urine is excreted

FIGURE 6.9 ADH SECRETION AND ACTION

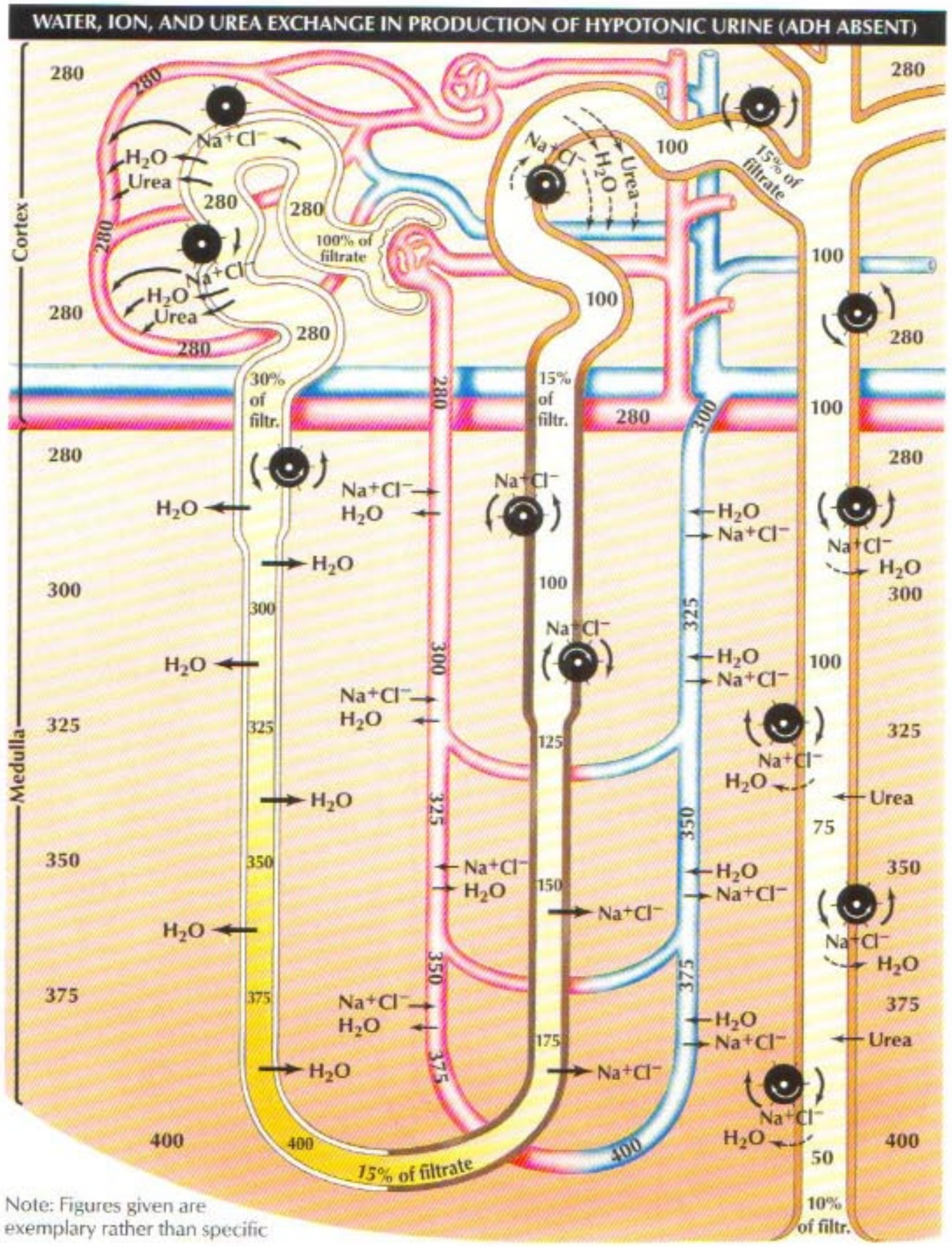
ADH regulates the volume of water excreted by the kidneys. Its secretion is regulated by the osmolality of the body fluids and the blood volume and pressure. Changes in body fluid osmolality of a few percent are sufficient to significantly alter ADH secretion. Decreases in blood volume and pressure of 10% to 15% or more are needed to effect ADH secretion. The blood volume and pressure sensors are found in the large pulmonary vessels, the carotid sinus, and the aortic arch. These "baroreceptors" respond to stretch of the vessel wall, which in turn is dependent on blood volume and pressure.


WATER, ION, AND UREA EXCHANGE IN PRODUCTION OF HYPERTONIC URINE (ADH PRESENT)
Cortex
Medulla
285
285
285
285
285
285
285
285
Na^+Cl^-
H_2O
Urea
Na^+Cl^-
H_2O
Urea
100% of filtrate
30% of filtr.
15% of filtr.
Na^+Cl^-
H_2O
Urea
100
100
15% of filtrate
H_2O
200
ADH
285
Na^+Cl^-
285
300
H_2O
Urea
300
Na^+Cl^-
Urea
H_2O
100
H_2O
Urea
Na^+Cl^-
Na^+Cl^-
H_2O
Urea
ADH
Na^+Cl^-
H_2O
Urea
Urea
H_2O
Na^+Cl^-
Urea
H_2O
325
Na^+Cl^-
H_2O
Urea
Na^+Cl^-
525
525
525
525
525
ADH
Na^+Cl^-
H_2O
Urea
Urea
H_2O
Na^+Cl^-
Urea
H_2O
550
H_2O
Urea
Na^+Cl^-
750
750
750
750
ADH
Na^+Cl^-
H_2O
Urea
Urea
Na^+Cl^-
Urea
H_2O
Na^+Cl^-
Urea
H_2O
775
Urea
Na^+Cl^-
H_2O
Urea
Na^+Cl^-
975
975
975
975
975
ADH
Urea
H_2O
Na^+Cl^-
H_2O
Urea
1200
1200
1000
15% of filtrate
1200
1200
1200
1% of filtr.

Note: Figures given are exemplary rather than specific

FIGURE 6.10 CONCENTRATION OF THE URINE

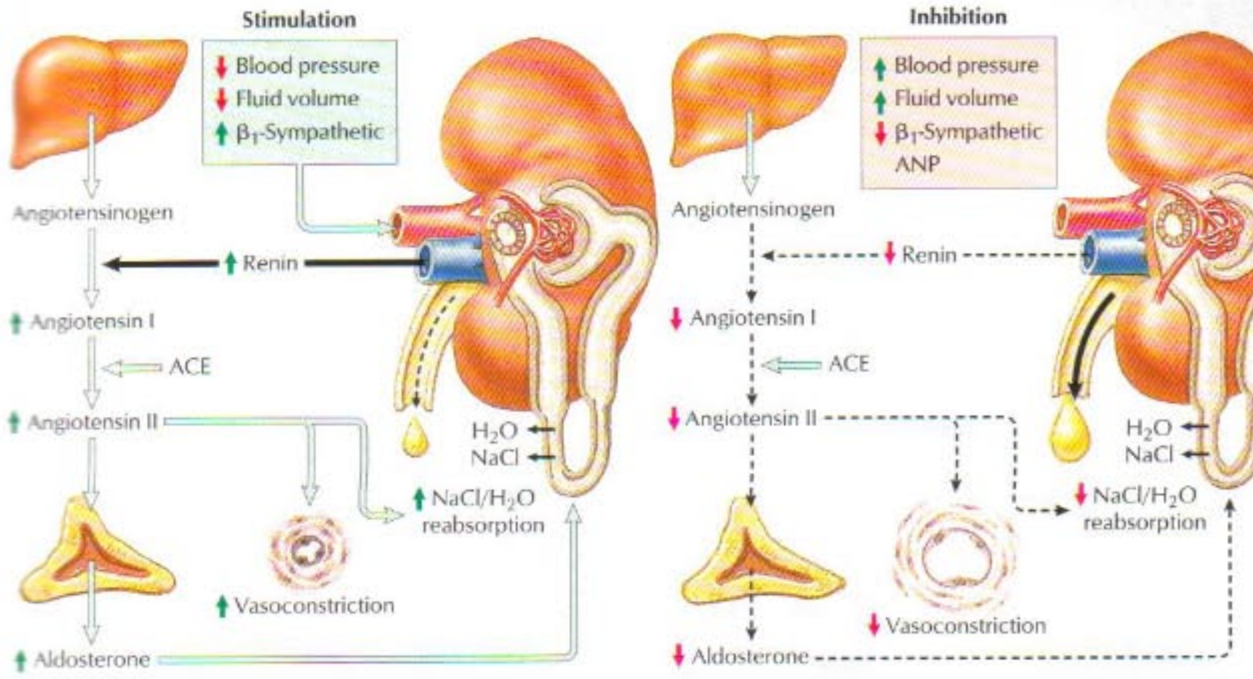
The excretion of a concentrated urine requires normal function of the loop of Henle (in particular the thick ascending limb), a hyperosmotic medullary interstitium, the presence of high levels of ADH in the blood, and the normal response of the collecting duct to ADH (i.e., increased water permeability). Under optimal conditions, this results in the excretion of 0.5 L/day of urine having an osmolality of 1200 mOsm/kg H_2O.


WATER, ION, AND UREA EXCHANGE IN PRODUCTION OF HYPOTONIC URINE (ADH ABSENT)
Cortex
Medulla
280
280
280
300
325
350
375
400
Na+Cl−
H2O
Urea
100% of filtrate
30% of filtr.
15% of filtr.
15% of filtrate
15% of filtrate
10% of filtr.
100
125
150
175
75
50
Urea
Na+Cl−
H2O

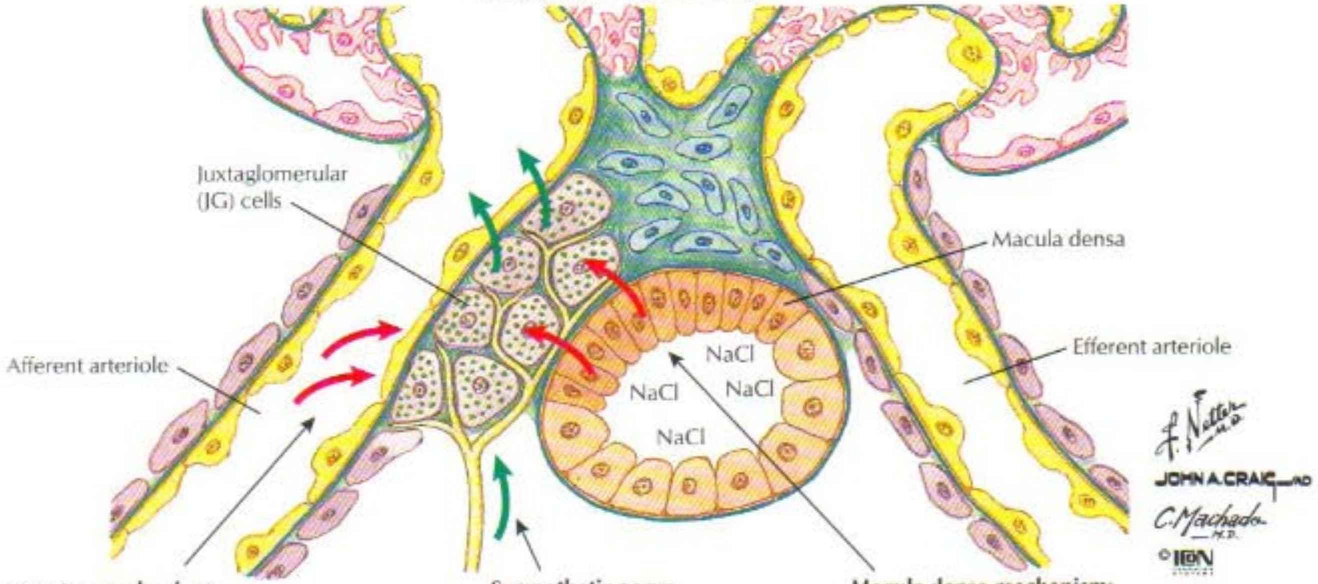
Note: Figures given are exemplary rather than specific

FIGURE 6.11 DILUTION OF THE URINE

The excretion of dilute urine requires normal function of the loop of Henle (especially the thick ascending limb) and the distal tubule, delivery of adequate amounts of tubule fluid to these segments, and the absence of ADH. Under optimal conditions, this results in the excretion of 18 L/day of urine having an osmolality of 50 mOsm/kg H_2O. Note that the osmolality of the medullary interstitium is reduced. This results from increased vasa recta blood flow (comp with Figure 6.10) and urea removal by the collecting duct.


Stimulation
↓ Blood pressure
↓ Fluid volume
↑ β_1-Sympathetic
Angiotensinogen
↑ Renin
↑ Angiotensin I
ACE
↑ Angiotensin II
H_2O
NaCl
↑ $NaCl/H_2O$ reabsorption
↑ Vasoconstriction
↑ Aldosterone
Inhibition
↑ Blood pressure
↑ Fluid volume
↓ β_1-Sympathetic
ANP
Angiotensinogen
↓ Renin
↓ Angiotensin I
ACE
↓ Angiotensin II
H_2O
NaCl
↓ $NaCl/H_2O$ reabsorption
↓ Vasoconstriction
↓ Aldosterone

Mechanisms of Renin Release


Juxtaglomerular (JG) cells
Macula densa
Afferent arteriole
Efferent arteriole
NaCl
NaCl
NaCl
NaCl
F. Netter M.D.
JOHN A.CRAIG AD
C.Machado M.D.
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Baroreceptor mechanism:
Increased pressure in afferent arteriole inhibits renin release from JG cells (red arrows); decreased pressure promotes renin release (green arrows)

Sympathetic nerve mechanism:
β_1-Adrenergic nerves stimulate renin release (green arrows)

Macula densa mechanism:
Increased NaCl in distal nephron inhibits renin release (red arrows); decreased load promotes renin release

FIGURE 6.12 RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The kidney synthesizes and secretes the proteolytic enzyme renin in response to decreased blood pressure and fluid volume (*upper panel*). Renin release ultimately results in increased levels of angiotensin II (AII) and aldosterone, both of which stimulate NaCl and water reabsorption by the nephron (AII acts on the proximal tubule and aldosterone acts on the collecting duct). AII is also a potent vasoconstrictor. Thus, when blood pressure and fluid volume are low, the renin-angiotensin-aldosterone system acts to restore both. The renin-secreting juxtaglomerular cells are located primarily in the afferent arteriole (*lower panel*). These cells respond directly to changes in arterial pressure, alterations in sympathetic nerve activity, and to the delivery of NaCl to the macula densa. *Abbreviations: ACE,* Angiotensin-converting enzyme; *ANP,* atrial natriuretic peptide.

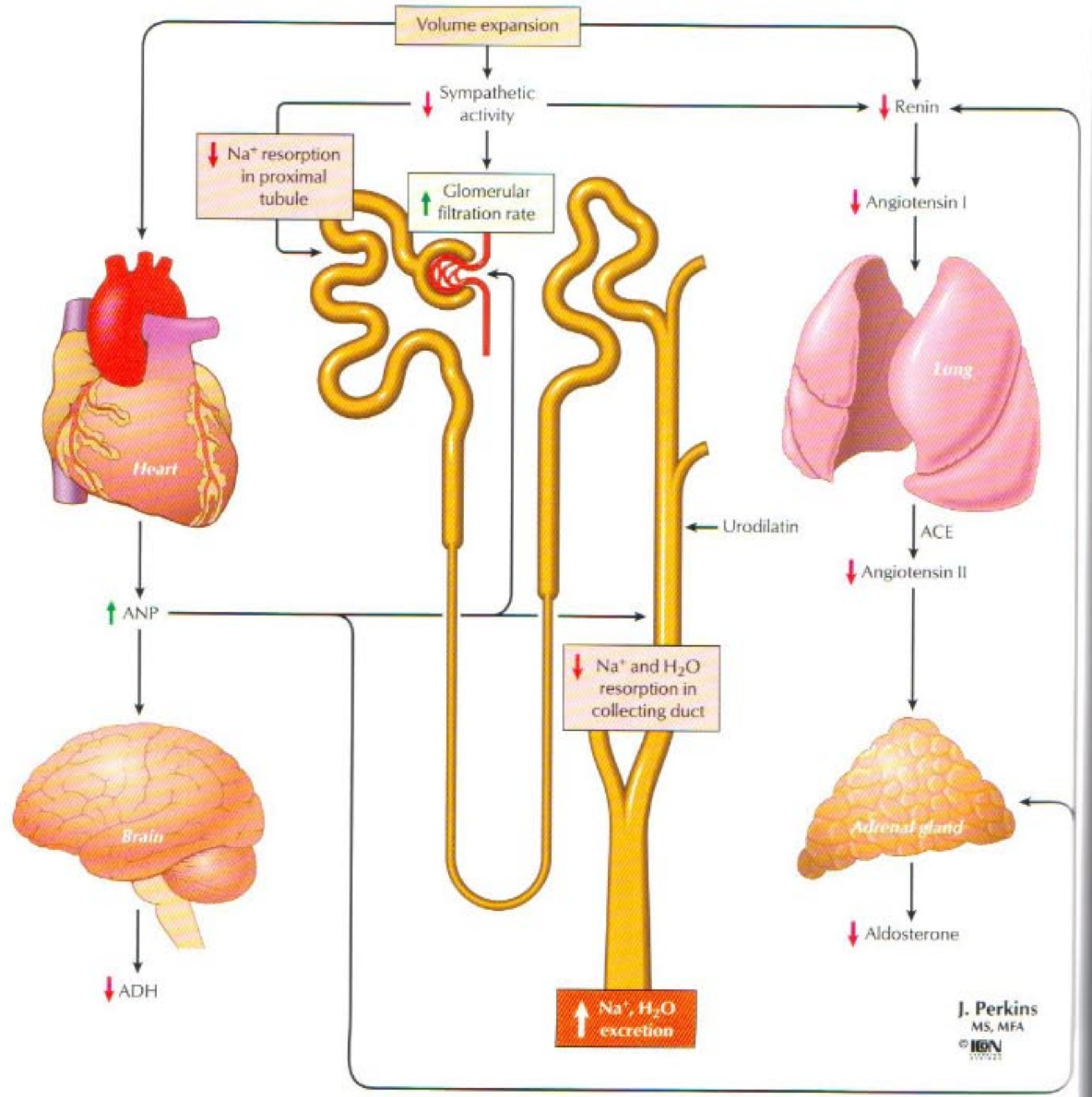
Volume expansion
↓ Sympathetic activity
↓ Renin
↓ Na⁺ resorption in proximal tubule
↑ Glomerular filtration rate
↓ Angiotensin I
Lung
Heart
Urodilatin
ACE
↓ Angiotensin II
↑ ANP
↓ Na⁺ and H₂O resorption in collecting duct
Brain
Adrenal gland
↓ Aldosterone
↓ ADH
↑ Na⁺, H₂O excretion
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FIGURE 6.13 RESPONSE TO VOLUME EXPANSION

The kidneys respond to an increase in the volume of the extracellular fluid (volume expansion) by increasing their excretion of NaCl and water. The primary mechanisms in this response are summarized. Enhanced NaCl excretion results from an increase in the filtered load of NaCl (increased GFR) and inhibition of NaCl reabsorption along the nephron. This occurs because the sympathetic and renin-angiotensin-aldosterone systems are suppressed and atrial natriuretic peptide (ANP) secretion is stimulated. The actions of ANP oppose those of the renin-angiotensin-aldosterone system. ANP increases GFR and inhibits collecting duct NaCl reabsorption. The kidney a produces its own natriuretic peptide called urodilatin, which contributes to this response. Decreased levels of antidiuretic hormone (ADH) cause increased water excretion. *Abbreviation: ACE,* Angiotensin-converting enzyme.

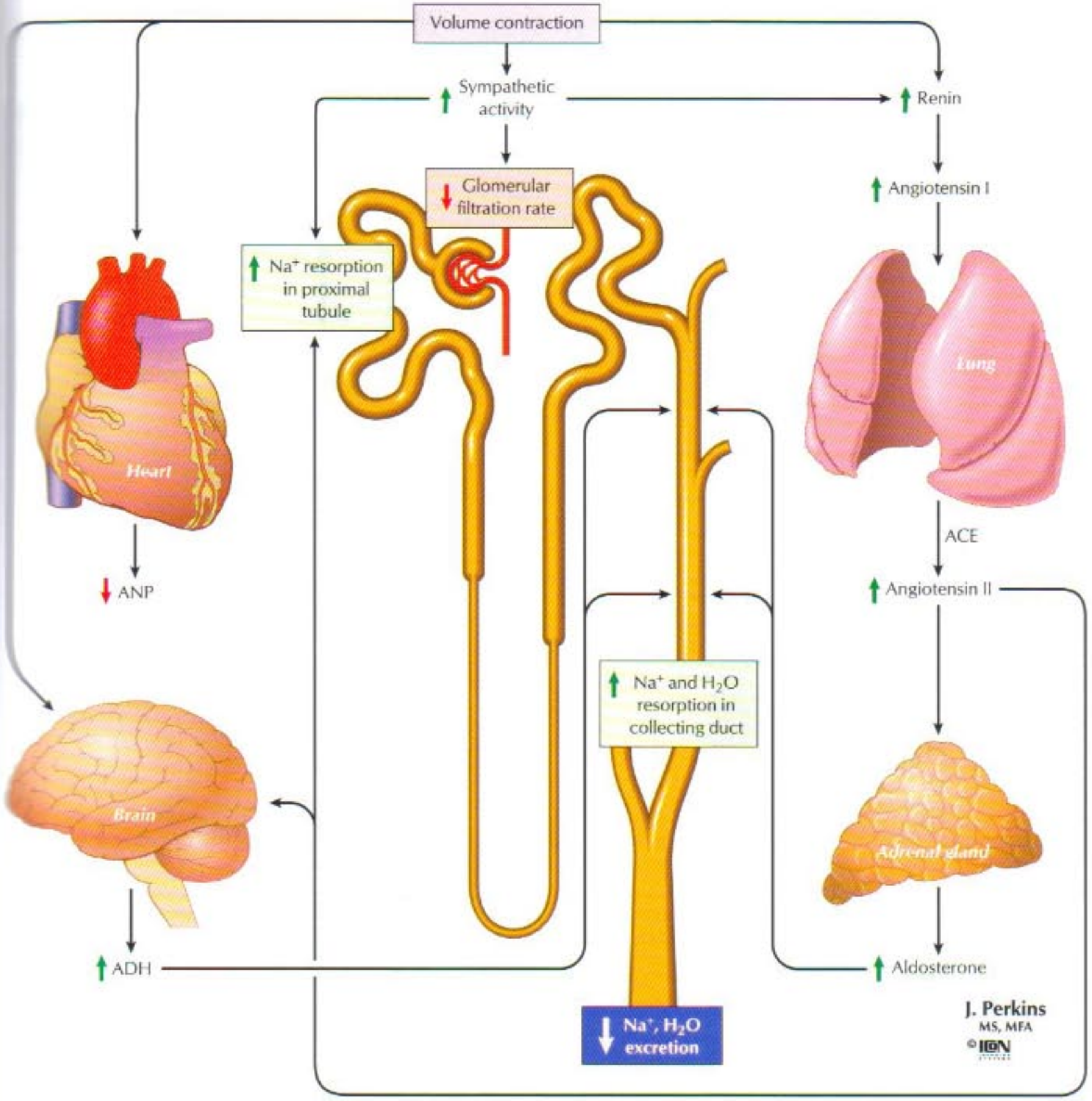
Volume contraction
↑ Sympathetic activity
↑ Renin
↓ Glomerular filtration rate
↑ Angiotensin I
↑ Na+ resorption in proximal tubule
Heart
Lung
ACE
↓ ANP
↑ Angiotensin II
↑ Na+ and H2O resorption in collecting duct
Brain
Adrenal gland
↑ ADH
↑ Aldosterone
↓ Na+, H2O excretion
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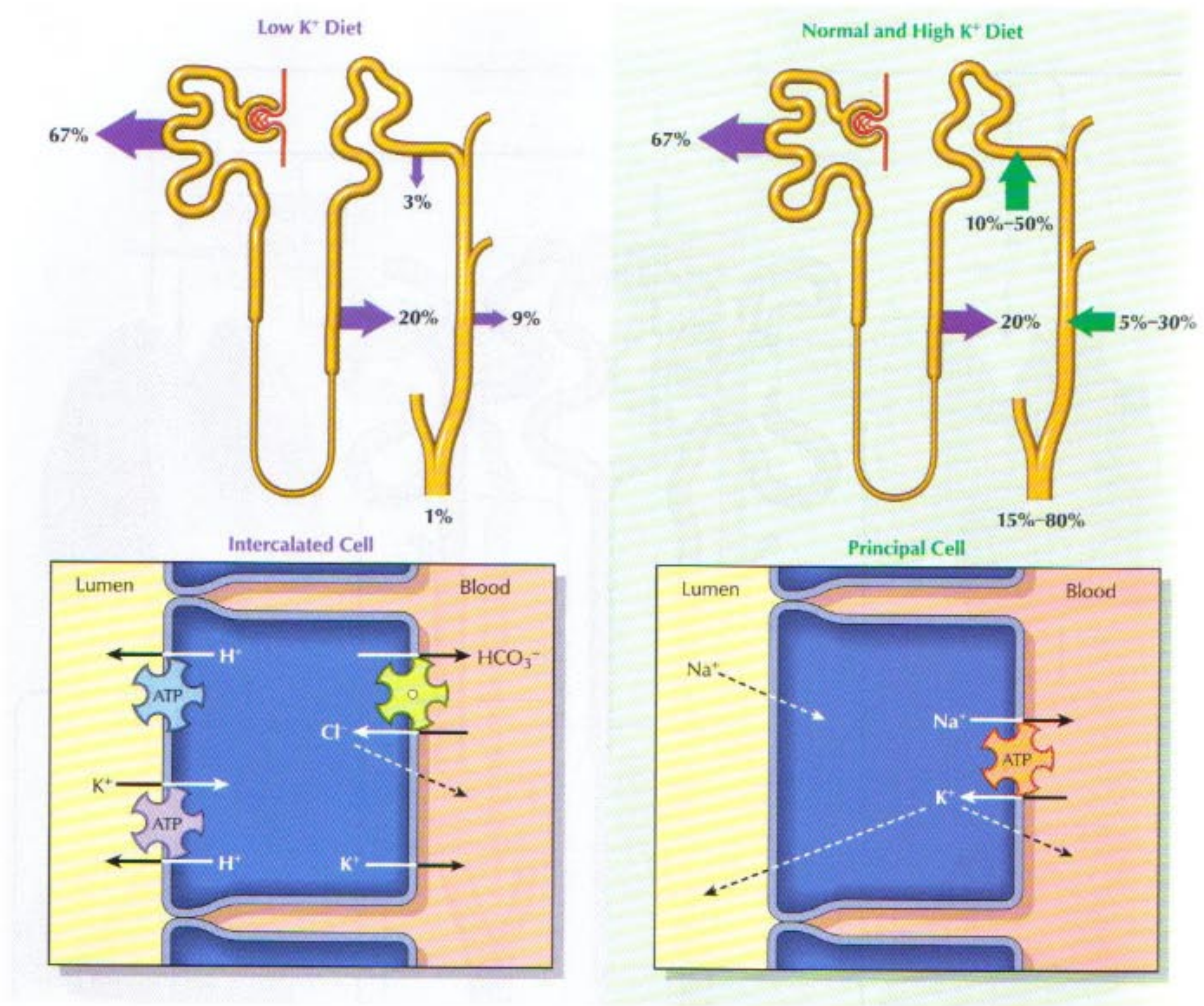
FIGURE 6.14 RESPONSE TO VOLUME CONTRACTION

The kidneys respond to a decrease in the volume of the extracellular fluid (volume contraction) by decreasing their excretion of NaCl and water. The primary mechanisms in this response are summarized. Decreased NaCl excretion results from a decrease in the filtered load of NaCl (decreased GFR) and stimulation of NaCl reabsorption along the nephron. This occurs because the sympathetic and renin-angiotensin-aldosterone systems are activated and atrial natriuretic peptide (ANP) secretion is suppressed. The sympathetic and renin-angiotensin-aldosterone systems decrease the GFR and stimulate proximal tubule and collecting duct NaCl reabsorption. Increased levels of antidiuretic hormone (ADH) cause decreased water excretion. *Abbreviation: ACE,* Angiotensin-converting enzyme.


Low K⁺ Diet
67%
3%
20%
9%
1%
Normal and High K⁺ Diet
67%
10%–50%
20%
5%–30%
15%–80%
Intercalated Cell
Lumen
Blood
H⁺
ATP
HCO₃⁻
Cl⁻
K⁺
ATP
H⁺
K⁺
Principal Cell
Lumen
Blood
Na⁺
Na⁺
ATP
K⁺

Physiologic Factors That Stimulate K⁺ Secretion	Physiologic Factors That Stimulate K⁺ Reabsorption	Factors That Alter K⁺ Secretion (Stimulate)	Factors That Alter K⁺ Secretion (Inhibit)
Aldosterone Hyperkalemia	Low K⁺ diet	Increased urine flow rate Acute and chronic alkalosis Chronic acidosis	Acute acidosis

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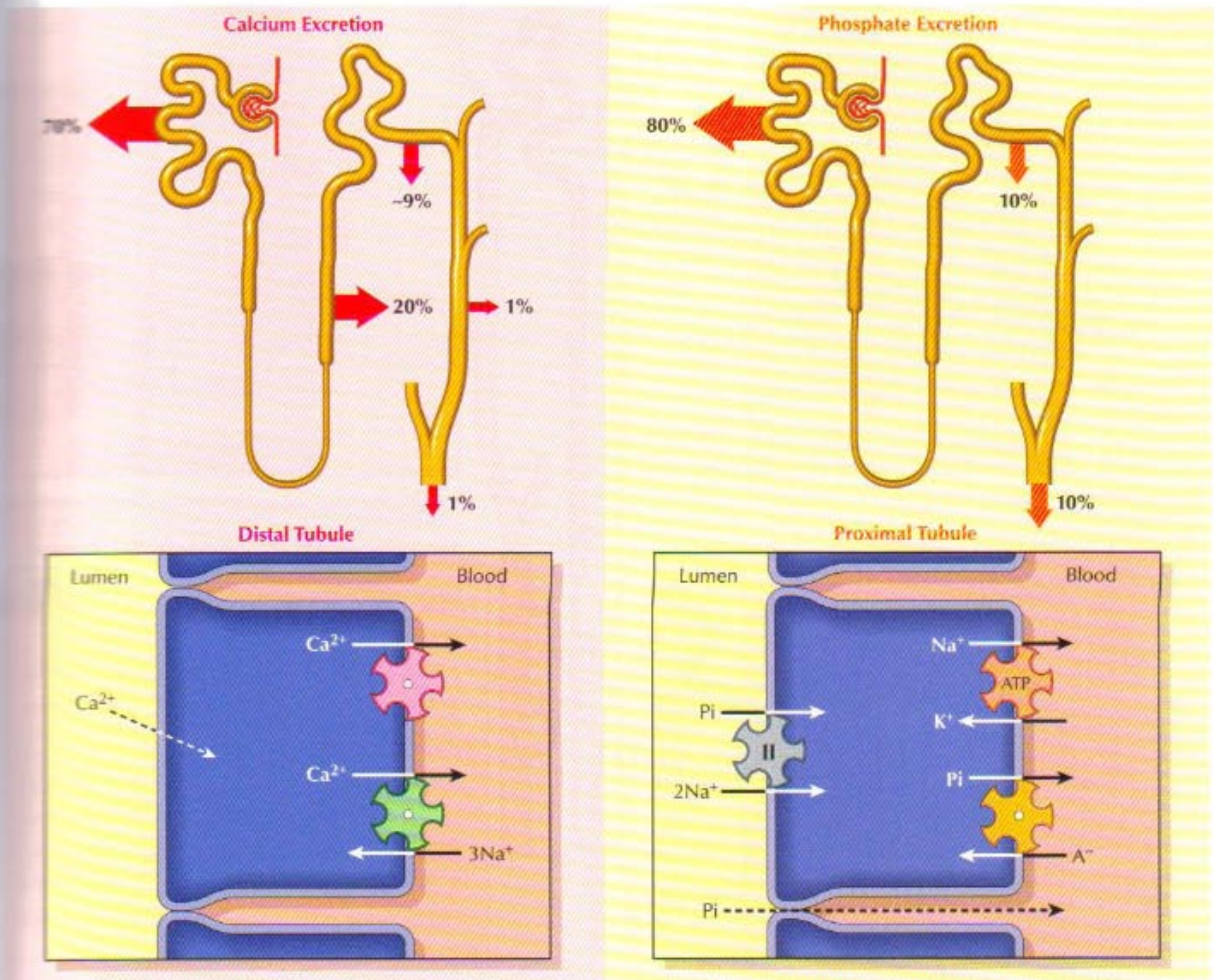
FIGURE 6.15 POTASSIUM EXCRETION

The kidneys are the primary route for excretion of K⁺ from the body, and the amount excreted varies with dietary K⁺ intake. On a low K⁺ diet, only about 1% of the filtered load is excreted. With a normal or high K⁺ diet, varying amounts of K⁺ are excreted. Most of the K⁺ that is excreted under these conditions reflects K⁺ that is secreted into the tubular fluid by the collecting duct. The principal cell of the collecting duct secretes K⁺, while the intercalated cell of the collectin duct is thought to be involved in K⁺ reabsorption during a low K⁺ diet. The mechanisms of K⁺ reabsorption by the proximal tubule an thick ascending limb of Henle's loop are depicted in Figure 6.8, an these are not influenced by dietary K⁺.


Calcium Excretion
70%
~9%
20%
1%
1%
Distal Tubule
Lumen
Blood
Ca^{2+}
Ca^{2+}
Ca^{2+}
$3Na^+$
Phosphate Excretion
80%
10%
10%
Proximal Tubule
Lumen
Blood
Na^+
ATP
K^+
Pi
Pi
$2Na^+$
Pi
A^-
Pi

Modulation of Ca^{2+} Transport
(Decreased Excretion)

Factor	Nephron Site	Mechanism
↑ PTH	DCT	Activate Ca^{2+} channels
↓ ECF	Proximal tubule	Solvent drag
↑ Pi intake	DCT	↑ PTH secretion

Modulation of Pi Transport
(Increased Excretion)

Factor	Nephron Site	Mechanism
↑ PTH	Proximal tubule	Apical symporter
↓ ECF	Proximal tubule	Solvent drag/symporter
↑ Pi intake	Proximal tubule	Apical symporter

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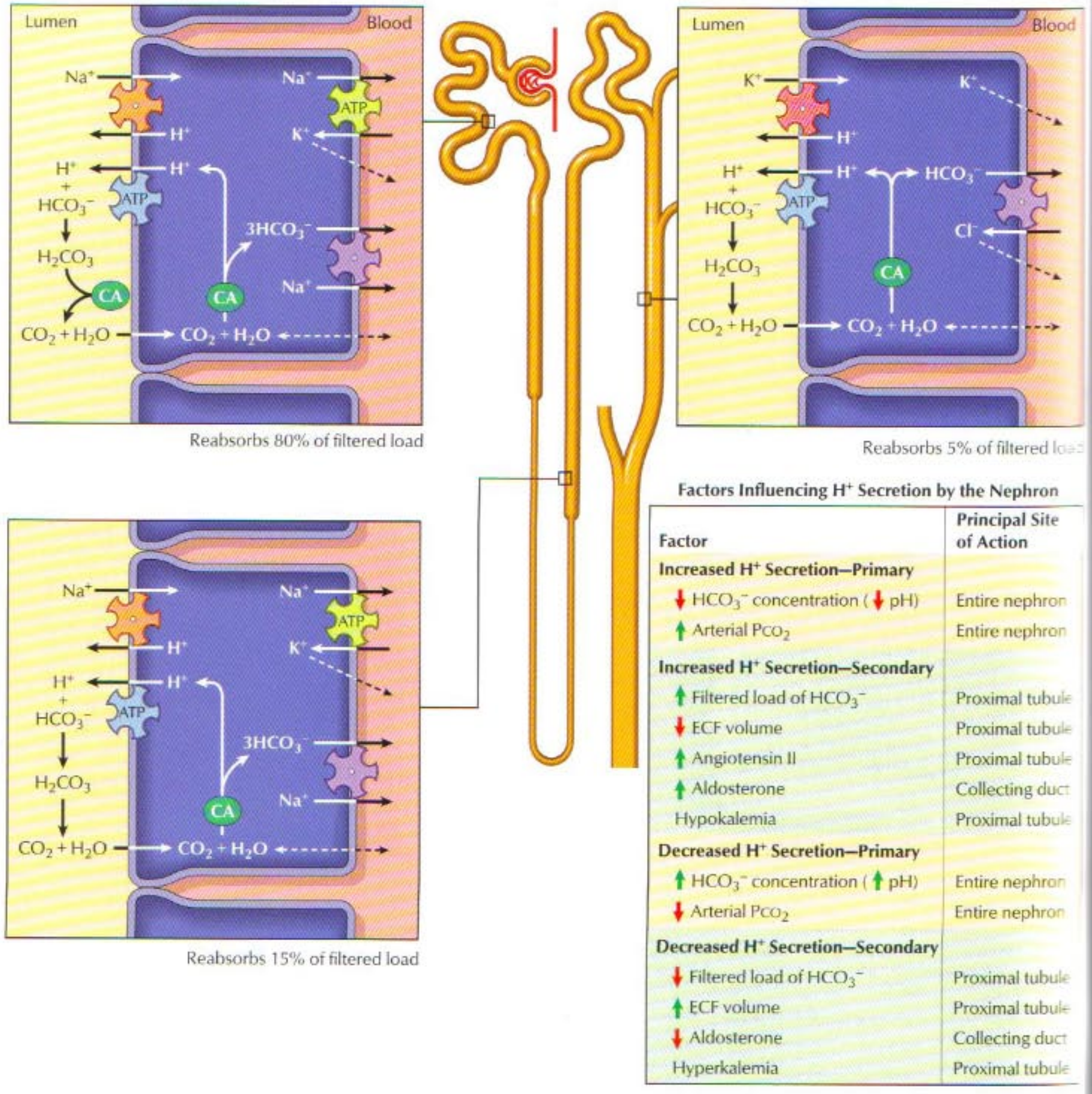
FIGURE 6.16 CALCIUM AND PHOSPHATE EXCRETION

Calcium is reabsorbed along the entire nephron. Its excretion is regulated by parathyroid hormone (PTH), which acts on cells of the distal tubule to stimulate reabsorption. Changes in the extracellular fluid (ECF) volume also effect Ca^{2+} excretion. However, this reflects changes in NaCl reabsorption by the proximal tubule in response to changes in ECF volume (see Figures 6.13 and 6.14) and is not directed at maintaining Ca^{2+} balance. Phosphate is primarily reabsorbed by the proximal tubule. Its excretion is also regulated by PTH, which acts on the proximal tubule to inhibit phosphate reabsorption. Changes in the ECF volume also affect phosphate excretion. However, like Ca^{2+}, this reflects changes in NaCl reabsorption by the proximal tubule in response to changes in ECF and is not directed at maintaining phosphate balance.



Reabsorbs 80% of filtered load

Reabsorbs 5% of filtered load

Reabsorbs 15% of filtered load

Factors Influencing H^+ Secretion by the Nephron

Factor	Principal Site of Action
Increased H^+ Secretion—Primary	
↓ HCO_3^- concentration (↓ pH)	Entire nephron
↑ Arterial P_{CO_2}	Entire nephron
Increased H^+ Secretion—Secondary	
↑ Filtered load of HCO_3^-	Proximal tubule
↓ ECF volume	Proximal tubule
↑ Angiotensin II	Proximal tubule
↑ Aldosterone	Collecting duct
Hypokalemia	Proximal tubule
Decreased H^+ Secretion—Primary	
↑ HCO_3^- concentration (↑ pH)	Entire nephron
↓ Arterial P_{CO_2}	Entire nephron
Decreased H^+ Secretion—Secondary	
↓ Filtered load of HCO_3^-	Proximal tubule
↑ ECF volume	Proximal tubule
↓ Aldosterone	Collecting duct
Hyperkalemia	Proximal tubule

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Figure 6.17 HCO_3^- Reabsorption

Bicarbonate is freely filtered and reabsorbed by the process of H^+ secretion along the nephron. Normally, all the filtered HCO_3^- is reabsorbed and none appears in the urine. Changes in systemic acid-base balance are the primary factors that regulate H^+ secretion. However, a number of other factors can also influence the kidney's ability to secrete H^+ and thus reabsorb HCO_3^-.

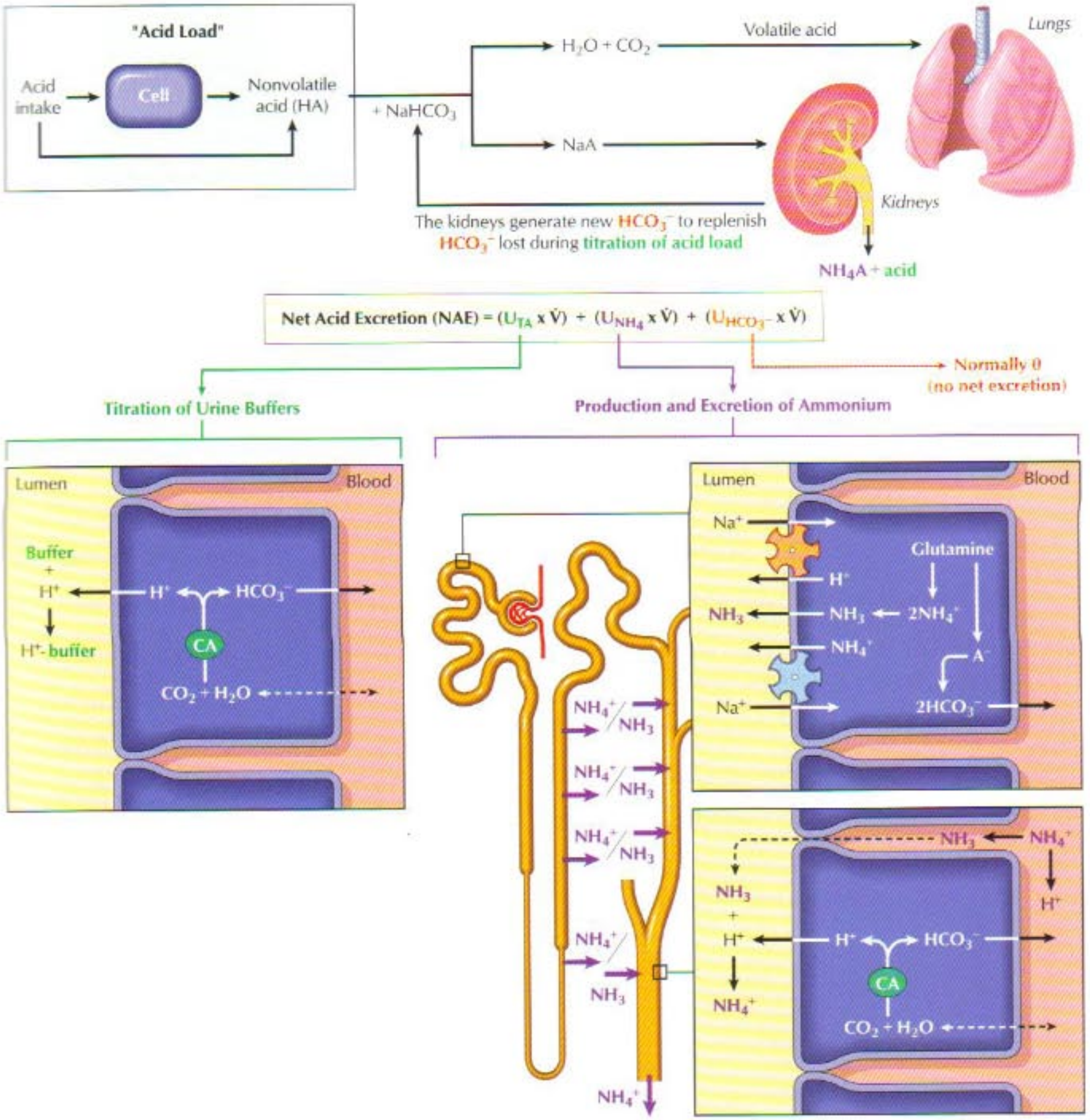
"Acid Load"
Acid intake
Cell
Nonvolatile acid (HA)
+ $NaHCO_3$
$H_2O + CO_2$
Volatile acid
Lungs
NaA
Kidneys
The kidneys generate new HCO_3^- to replenish HCO_3^- lost during titration of acid load
NH_4A + acid
Net Acid Excretion (NAE) = $(U_{TA} \times \dot{V}) + (U_{NH_4} \times \dot{V}) + (U_{HCO_3^-} \times \dot{V})$
Normally 0 (no net excretion)
Titration of Urine Buffers
Production and Excretion of Ammonium
Lumen
Blood
Buffer + H^+
H^+-buffer
H^+
HCO_3^-
CA
$CO_2 + H_2O$
Na^+
Glutamine
NH_3
$2NH_4^+$
NH_4^+
A^-
$2HCO_3^-$
NH_4^+/NH_3
$NH_3 + H^+$
NH_4^+

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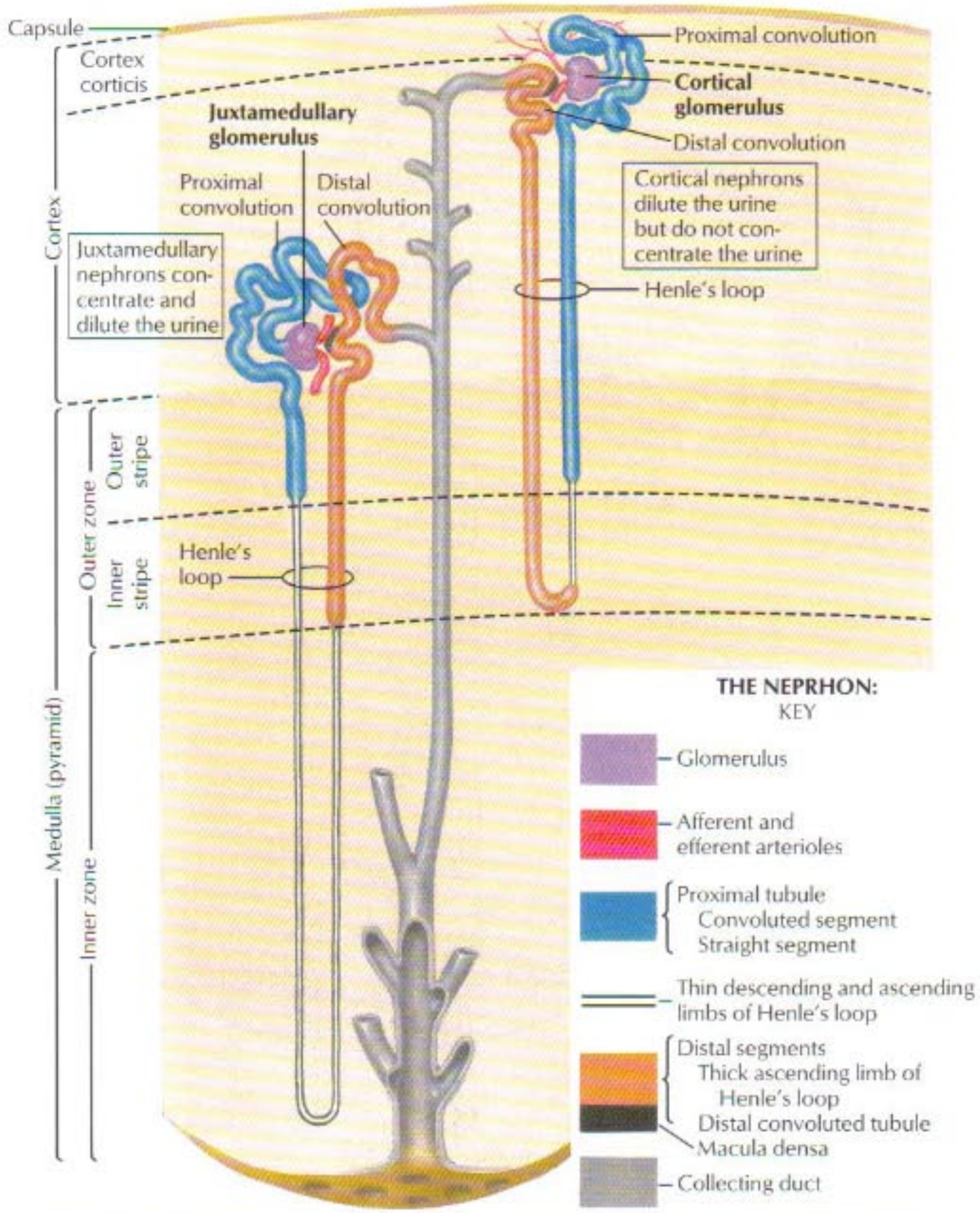
FIGURE 6.18 RENAL PRODUCTION OF NEW HCO_3^-

The kidneys generate new HCO_3^- to replenish that which is lost during the titration of the daily acid load. This occurs by the process of net acid excretion (NAE). Normally, the entire filtered load of HCO_3^- is reabsorbed (see Figure 6.17), and none appears in the urine. This process does not produce new HCO_3^-, but simply prevents its loss from the body. New HCO_3^- is produced when the kidneys excrete H^+ with urinary buffers (the primary urine buffer is phosphate) and when the kidneys produce and excrete NH_4^+. The production and excretion of NH_4^+ is the most important component of NAE because these processes are regulated in response to acid-base disorders. Acidosis stimulates NH_4^+ production (from glutamine in the proximal tubule) and its excretion, whereas alkalosis inhibits these process. Acid-base balance is maintained when NAE is the same as the daily acid load, which is approximately 1 mEq/kg body weight/day. *Abbreviations:* U_{TA}, Urine concentration of titratable acid; U_{NH_4}, urine concentration of ammonium; U_{HCO_3}, urine concentration of bicarbonate; $\dot{V}$ = urine flow rate.


Capsule
Cortex corticis
Cortex
Juxtamedullary glomerulus
Proximal convolution
Distal convolution
Juxtamedullary nephrons concentrate and dilute the urine
Outer zone
Outer stripe
Inner stripe
Henle's loop
Medulla (pyramid)
Inner zone
Proximal convolution
Cortical glomerulus
Distal convolution
Cortical nephrons dilute the urine but do not concentrate the urine
Henle's loop
THE NEPRHON:
KEY
Glomerulus
Afferent and efferent arterioles
Proximal tubule
Convoluted segment
Straight segment
Thin descending and ascending limbs of Henle's loop
Distal segments
Thick ascending limb of Henle's loop
Distal convoluted tubule
Macula densa
Collecting duct

Renal blood flow	1–1.2 L/min	Number of nerphons	2.5 million
Glomerular filtration	100–125 mL/min	Cortical	2.1 million
rate	140–180 L/day	Juxtamedullary	0.4 million
Urine flow rate	0.5–18 L/day		

FIGURE 6.2 ANATOMY OF THE NEPHRON

The nephrons of the kidney differ somewhat in structure depending on the location of their glomerulus. Cortical nephrons have their glomeruli in the upper or superficial portion of the cortex. These cortical nephrons have short loops of Henle that extend only into the outer zone of the medulla. The glomeruli of juxtamedullary nephrons are located at the corticomedullary junction. These nephrons have long loops of Henle that extend deep into the inner zone of the medulla. There are many more cortical than juxtamedullary nephrons.

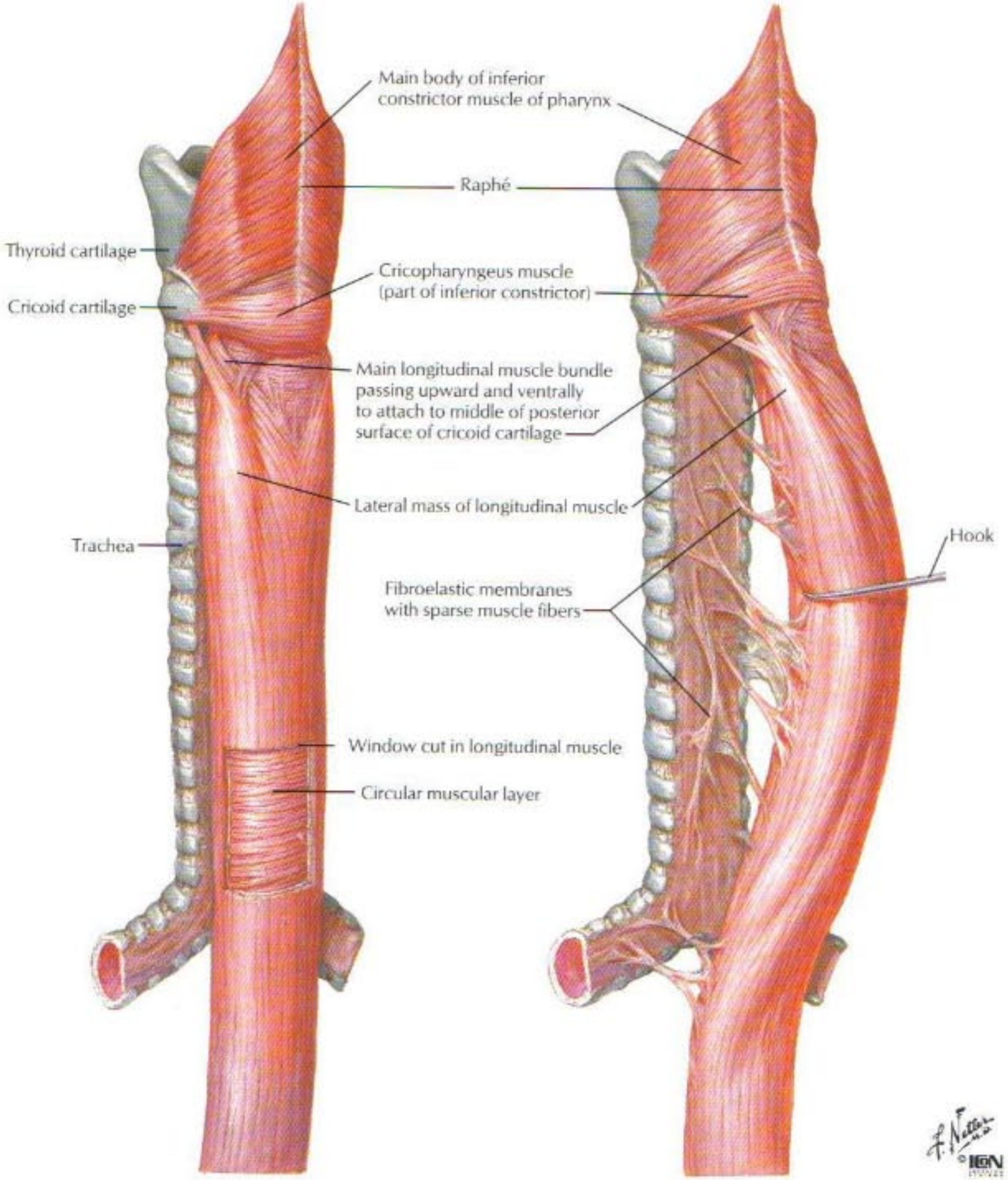

Main body of inferior constrictor muscle of pharynx
Raphé
Thyroid cartilage
Cricoid cartilage
Cricopharyngeus muscle (part of inferior constrictor)
Main longitudinal muscle bundle passing upward and ventrally to attach to middle of posterior surface of cricoid cartilage
Lateral mass of longitudinal muscle
Trachea
Hook
Fibroelastic membranes with sparse muscle fibers
Window cut in longitudinal muscle
Circular muscular layer

FIGURE 7.1 ESOPHAGUS

The esophagus lies posterior to the trachea and extends from the oropharynx to the stomach. It propels food and fluid to the stomach by peristalsis. The muscle of the upper third of the esophagus is skeletal, the lower third is smooth muscle, and the middle third is mixed skeletal and smooth muscle. The muscular walls of the esophagus form an outer longitudinal and an inner circular layer.

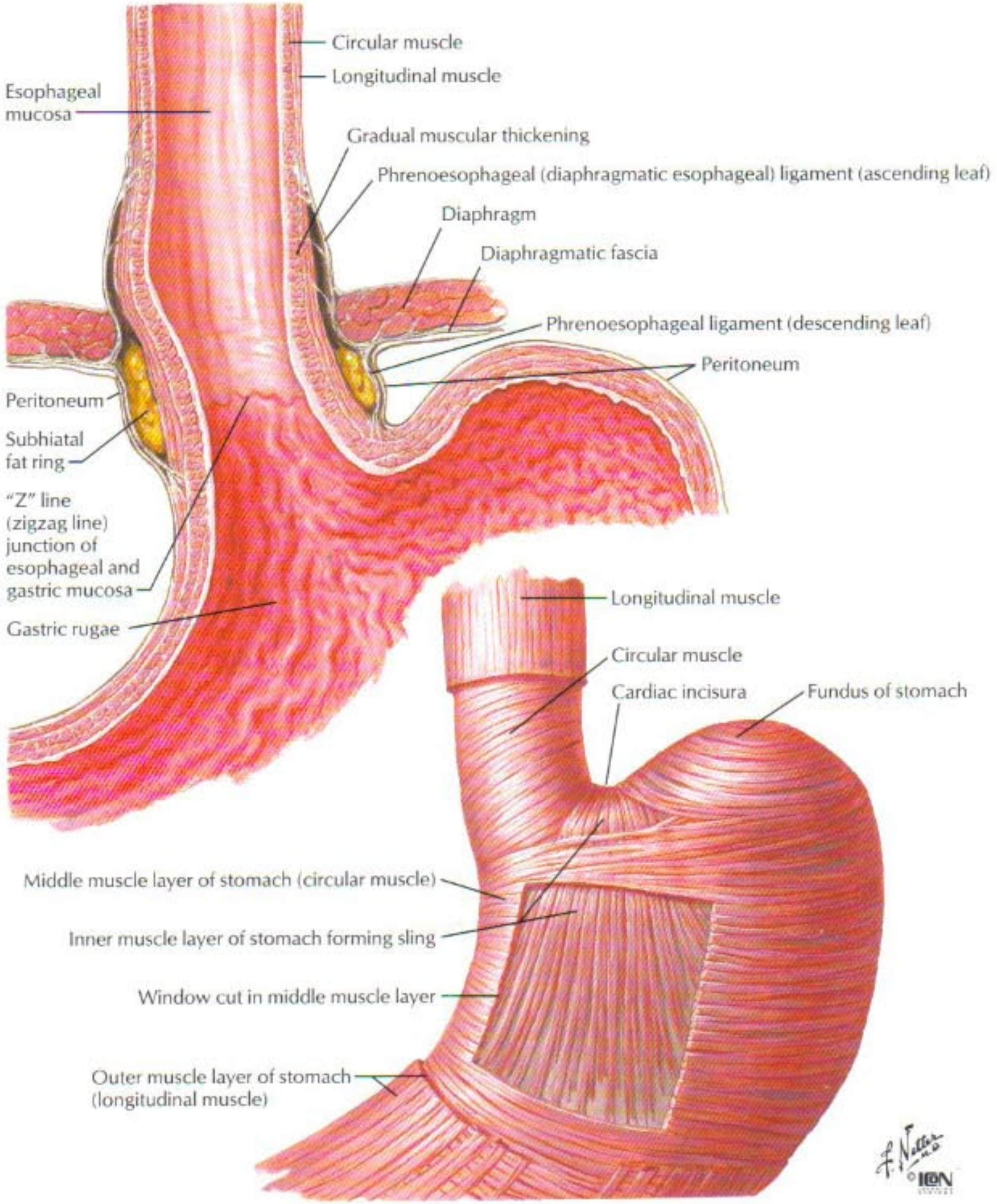

Circular muscle
Longitudinal muscle
Esophageal mucosa
Gradual muscular thickening
Phrenoesophageal (diaphragmatic esophageal) ligament (ascending leaf)
Diaphragm
Diaphragmatic fascia
Phrenoesophageal ligament (descending leaf)
Peritoneum
Peritoneum
Subhiatal fat ring
"Z" line (zigzag line) junction of esophageal and gastric mucosa
Gastric rugae
Longitudinal muscle
Circular muscle
Cardiac incisura
Fundus of stomach
Middle muscle layer of stomach (circular muscle)
Inner muscle layer of stomach forming sling
Window cut in middle muscle layer
Outer muscle layer of stomach (longitudinal muscle)
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FIGURE 7.2 GASTROESOPHAGEAL JUNCTION

The smooth muscle of the lower esophagus increases in thickness at the junction with the stomach and forms the lower esophageal sphincter (LES). The LES lies where the esophagus passes through the diaphragm, and at this point, the esophageal mucosa changes to gastric mucosa (Z line). The stomach has three muscle layers in its walls, and the most orad, or cardiac, portion of the stomach relaxes (receptive relaxation) to receive the food bolus from the esophagus.

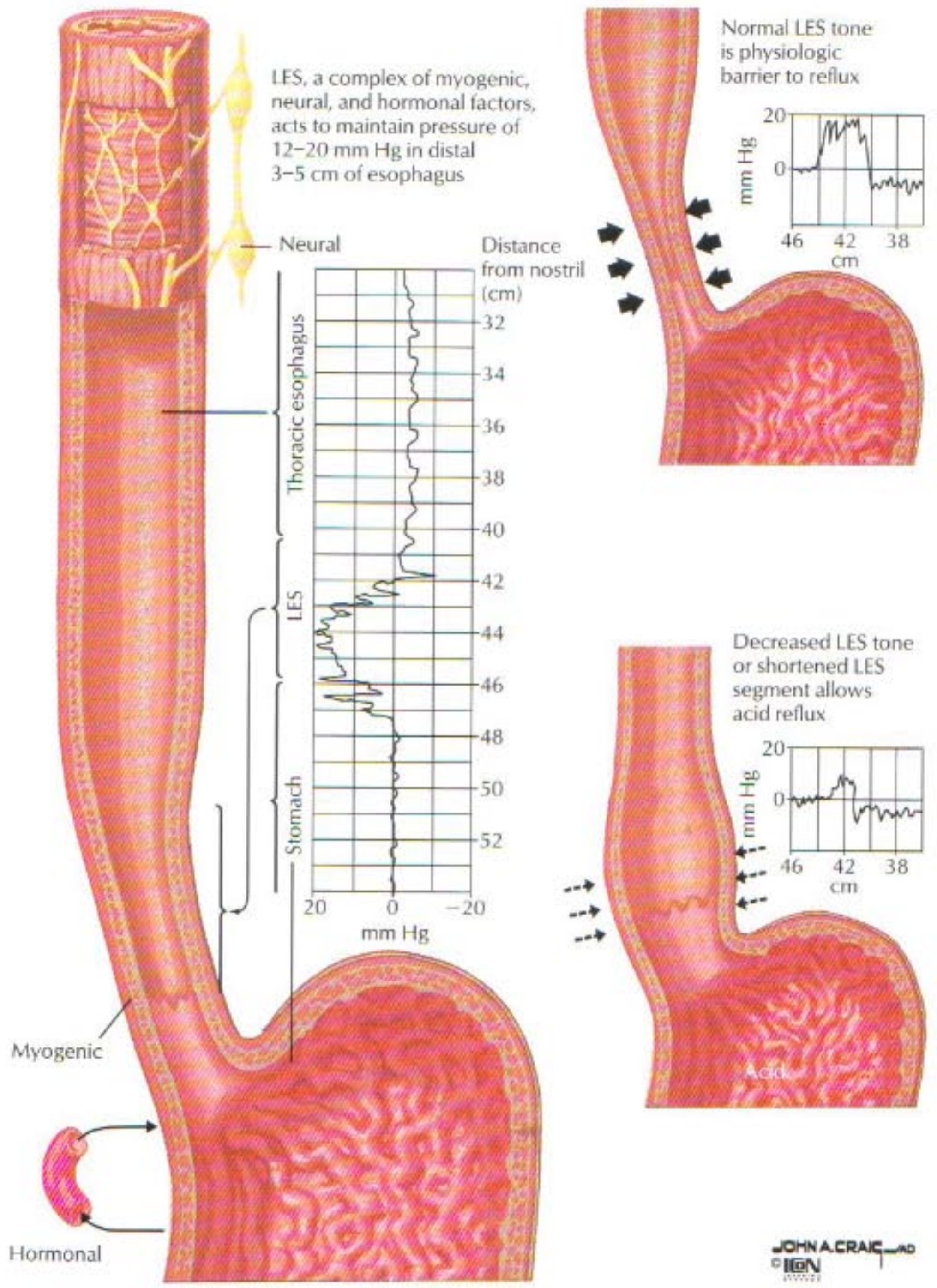
LES, a complex of myogenic, neural, and hormonal factors, acts to maintain pressure of 12–20 mm Hg in distal 3–5 cm of esophagus
Neural
Distance from nostril (cm)
32
34
36
38
40
42
44
46
48
50
52
Thoracic esophagus
LES
Stomach
20
0
−20
mm Hg
Myogenic
Hormonal
Normal LES tone is physiologic barrier to reflux
20
0
mm Hg
46
42
38
cm
Decreased LES tone or shortened LES segment allows acid reflux
20
0
mm Hg
46
42
38
cm
Acid
JOHN A.CRAIG_AD
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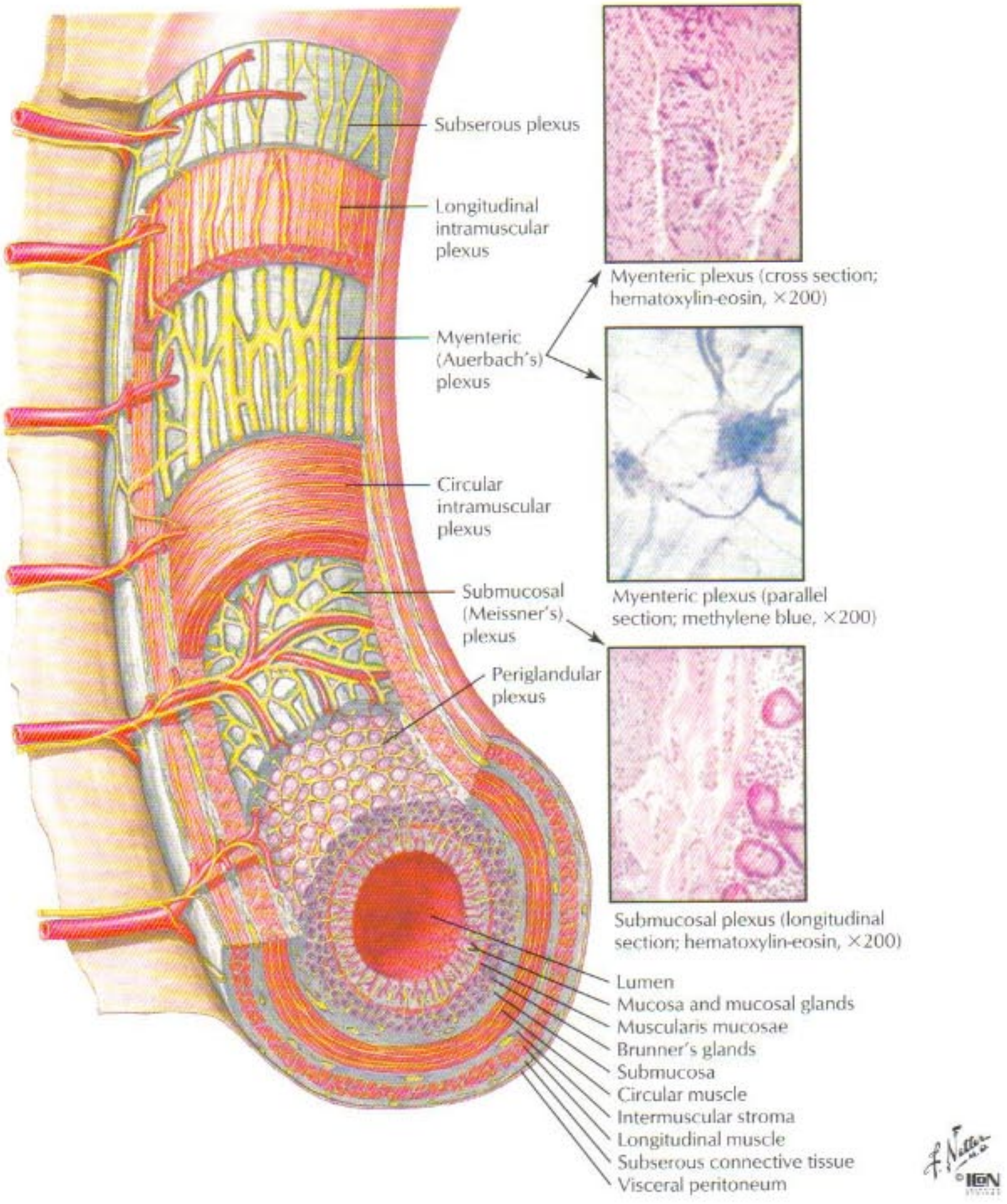
FIGURE 7.3 LOWER ESOPHAGEAL SPHINCTER

Peristalsis is initiated by the voluntary action of swallowing, which is controlled by efferent fibers in the vagus. Vagal fibers synapse on neurons within the myenteric plexus (enteric nervous system) of the esophagus. The myenteric plexus directly controls the peristaltic wave by alternatively relaxing then contracting the muscles of the esophagus. The smooth muscle increases in thickness at the junction with the stomach and forms the lower esophageal sphincter (LES). Normally, the resting tone of the LES is high, which prevents the reflux of gastric contents into the esophagus. As the peristaltic wave carries a bolus of food to the stomach, release of nitric oxide (NO) and vasoactive intestinal peptide (VIP) from neurons of the myenteric plexus causes relaxation of the LES, and food enters the stomach.


Subserous plexus
Longitudinal intramuscular plexus
Myenteric (Auerbach's) plexus
Circular intramuscular plexus
Submucosal (Meissner's) plexus
Periglandular plexus
Lumen
Mucosa and mucosal glands
Muscularis mucosae
Brunner's glands
Submucosa
Circular muscle
Intermuscular stroma
Longitudinal muscle
Subserous connective tissue
Visceral peritoneum

Myenteric plexus (cross section; hematoxylin-eosin, ×200)

Myenteric plexus (parallel section; methylene blue, ×200)

Submucosal plexus (longitudinal section; hematoxylin-eosin, ×200)

FIGURE 7.4 ENTERIC NERVOUS SYSTEM

The intrinsic innervation of the small and large intestine is by the enteric nervous system, comprised of a neural network in the myenteric (Auerbach's) and submucosal (Meissner's) plexuses. The myenteric plexus is primarily involved in controlling motility, whereas the submucosal plexus primarily controls fluid secretion and absorption. Neurons of this system interconnect with one another and with the neuronal processes of the autonomic nervous system. Transmitter substances (more than 20 different ones have been identified) such as ACh (acetylcholine), substance P, 5-HT (serotonin), VIP (vasoactive intestinal peptide), NO (nitric oxide), somatostatin, and a host of other peptides are commonly found in the intrinsic neurons. For example, ACh and substance P are excitatory to smooth muscle, whereas VIP and NO are inhibitory. Optimal functioning of the GI tract requires coordinated interactions between a host of endocrine, paracrine, and neurocrine substances.

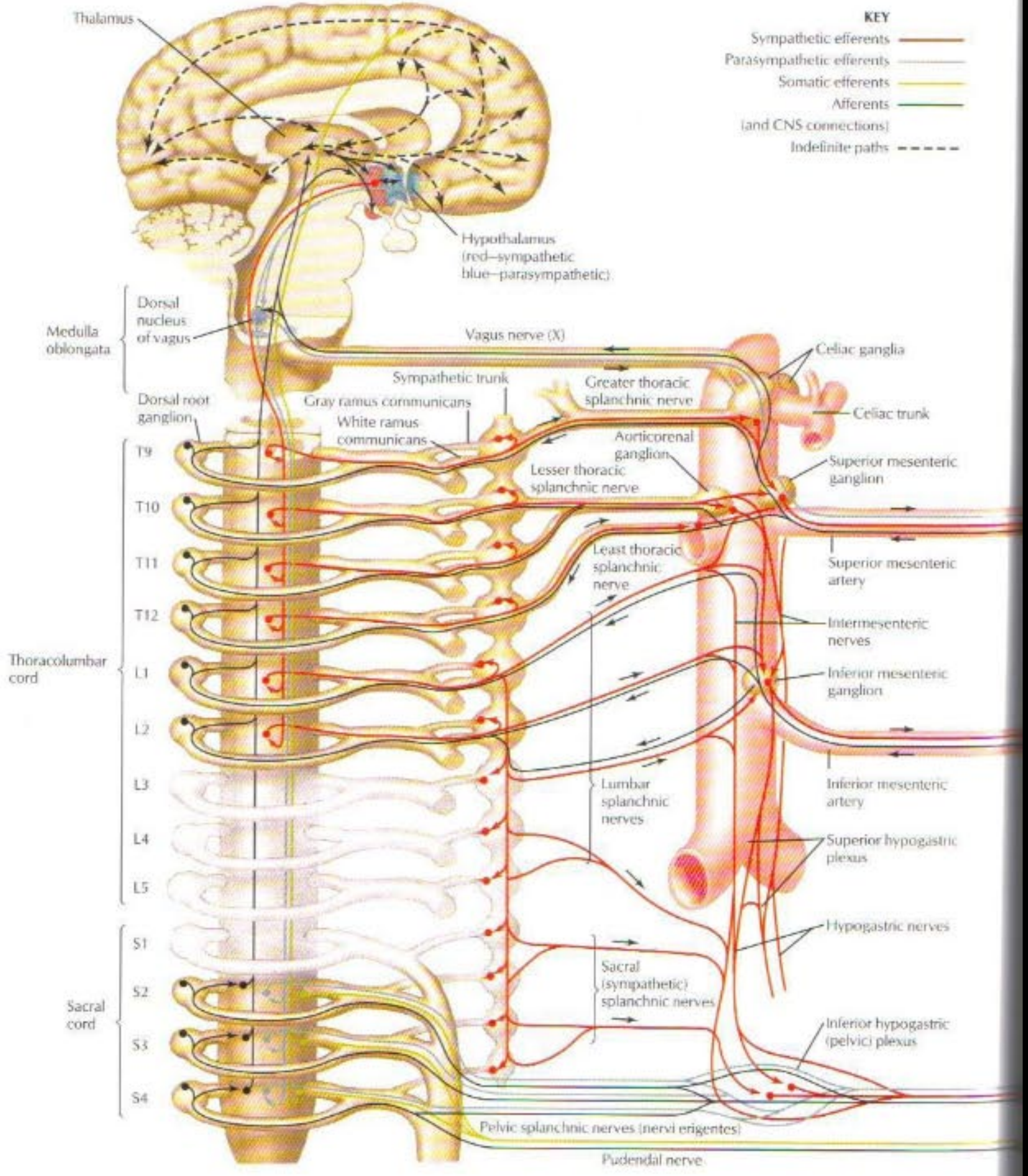
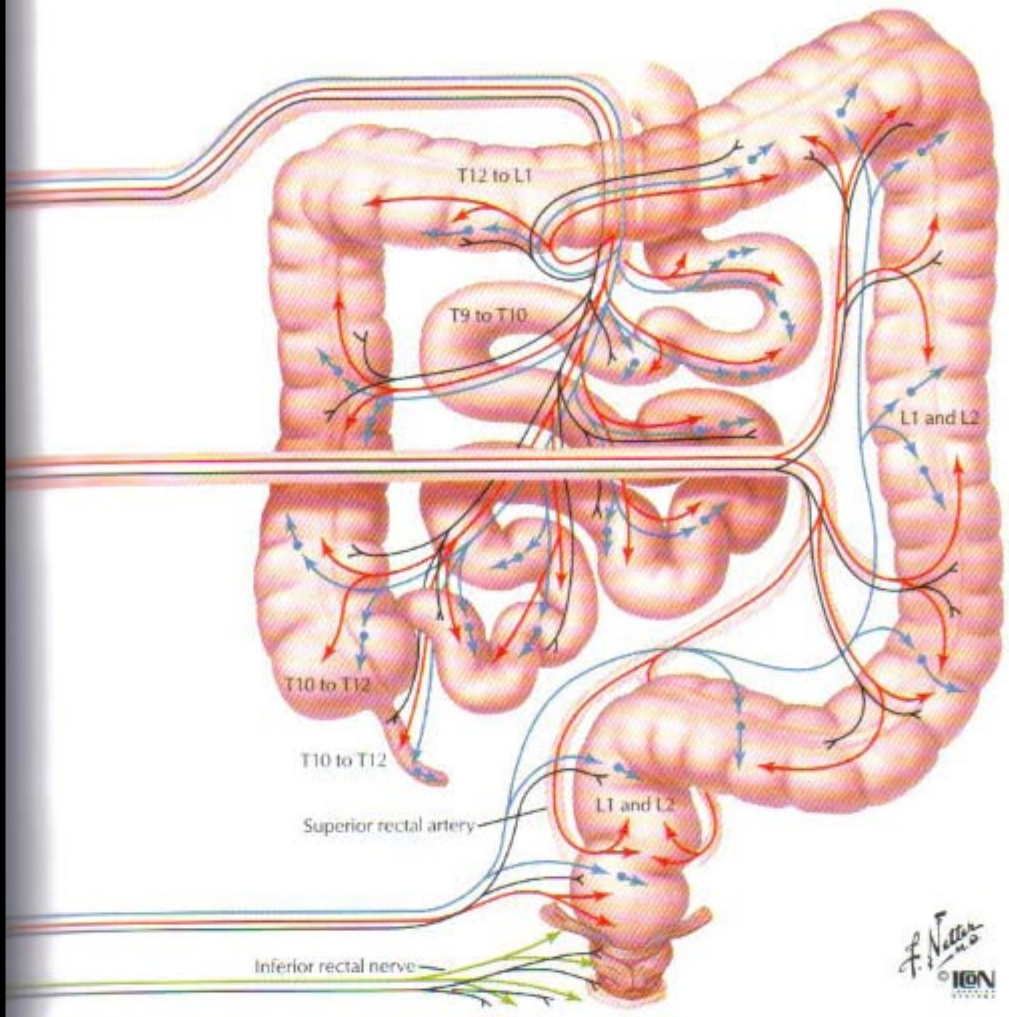

KEY
Sympathetic efferents
Parasympathetic efferents
Somatic efferents
Afferents
(and CNS connections)
Indefinite paths
Thalamus
Hypothalamus
(red—sympathetic
blue—parasympathetic)
Medulla oblongata
Dorsal nucleus of vagus
Vagus nerve (X)
Celiac ganglia
Celiac trunk
Sympathetic trunk
Greater thoracic splanchnic nerve
Dorsal root ganglion
Gray ramus communicans
White ramus communicans
Aorticorenal ganglion
Lesser thoracic splanchnic nerve
Superior mesenteric ganglion
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
Least thoracic splanchnic nerve
Superior mesenteric artery
Intermesenteric nerves
Thoracolumbar cord
Inferior mesenteric ganglion
Inferior mesenteric artery
Lumbar splanchnic nerves
Superior hypogastric plexus
Hypogastric nerves
Sacral (sympathetic) splanchnic nerves
Sacral cord
Inferior hypogastric (pelvic) plexus
Pelvic splanchnic nerves (nervi erigentes)
Pudendal nerve

FIGURE 7.5 AUTONOMIC INNERVATION

The innervation of the small and large intestines is by the sympathetic and parasympathetic fibers of the autonomic nervous system, which comprises the extrinsic innervation of the GI tract. Sympathetic fibers originate from the thoracolumbar spinal cord (T5–L2) and distribute to collateral ganglia (celiac, superior mesenteric, inferior mesenteric). Parasympathetic fibers come from the vagus and pelvic splanchnic nerves (S2–S4).


T12 to L1
T9 to T10
L1 and L2
T10 to T12
T10 to T12
L1 and L2
Superior rectal artery
Inferior rectal nerve
F. Netter M.D.
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In general, sympathetics decrease peristalsis and secretomotor activity (i.e., decreased fluid secretion), whereas parasympathetics increase peristalsis, relax involuntary sphincters, and increase secretomotor activity (i.e., increased fluid secretion). Feedback loops to the central nervous system, especially the hypothalamus and its cortical projections, integrate visceral function and coordinate activity between the extrinsic and intrinsic neurons of the bowel.

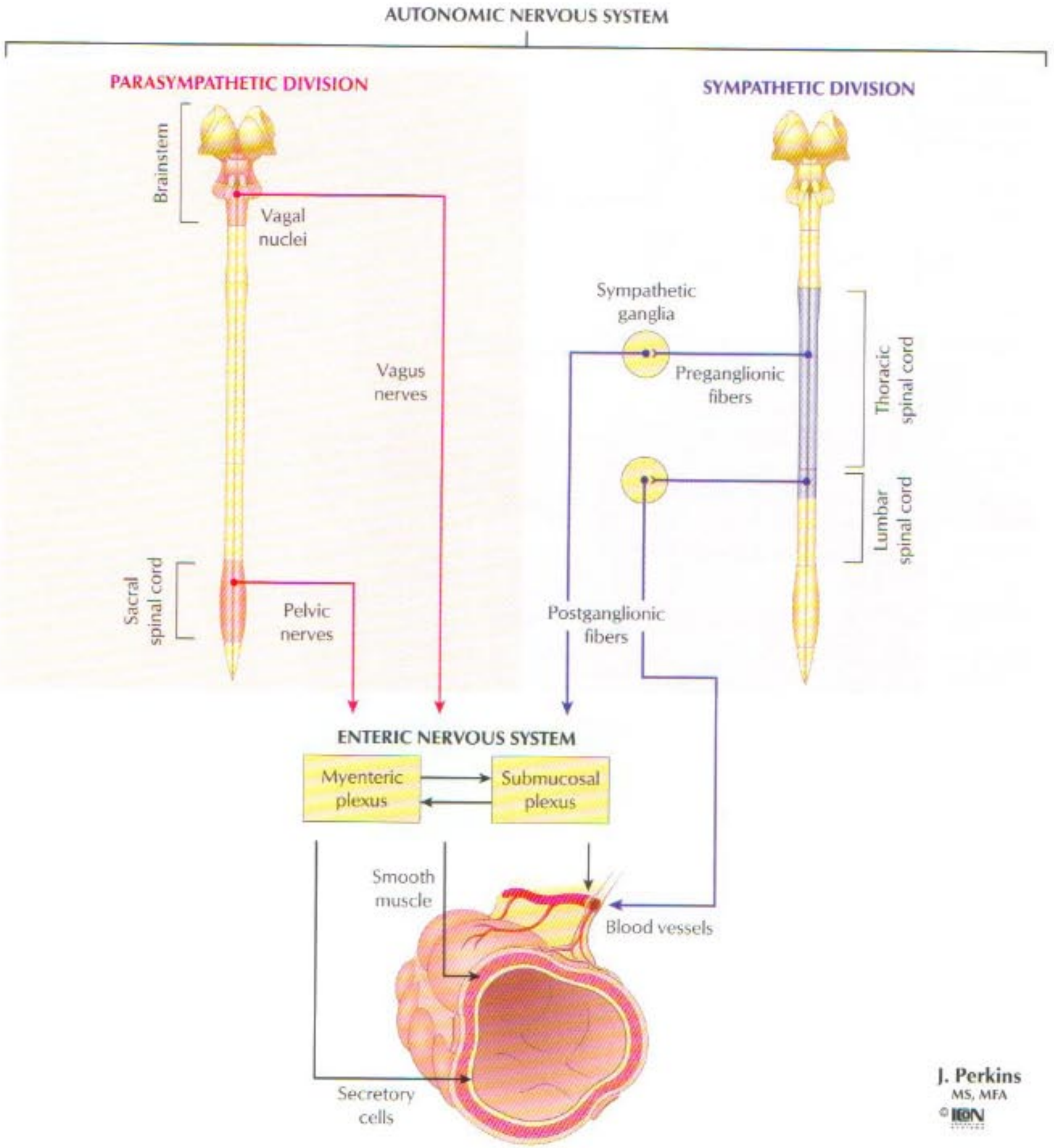
AUTONOMIC NERVOUS SYSTEM
PARASYMPATHETIC DIVISION
Brainstem
Vagal nuclei
Vagus nerves
Sacral spinal cord
Pelvic nerves
SYMPATHETIC DIVISION
Sympathetic ganglia
Preganglionic fibers
Thoracic spinal cord
Lumbar spinal cord
Postganglionic fibers
ENTERIC NERVOUS SYSTEM
Myenteric plexus
Submucosal plexus
Smooth muscle
Blood vessels
Secretory cells
J. Perkins
MS, MFA
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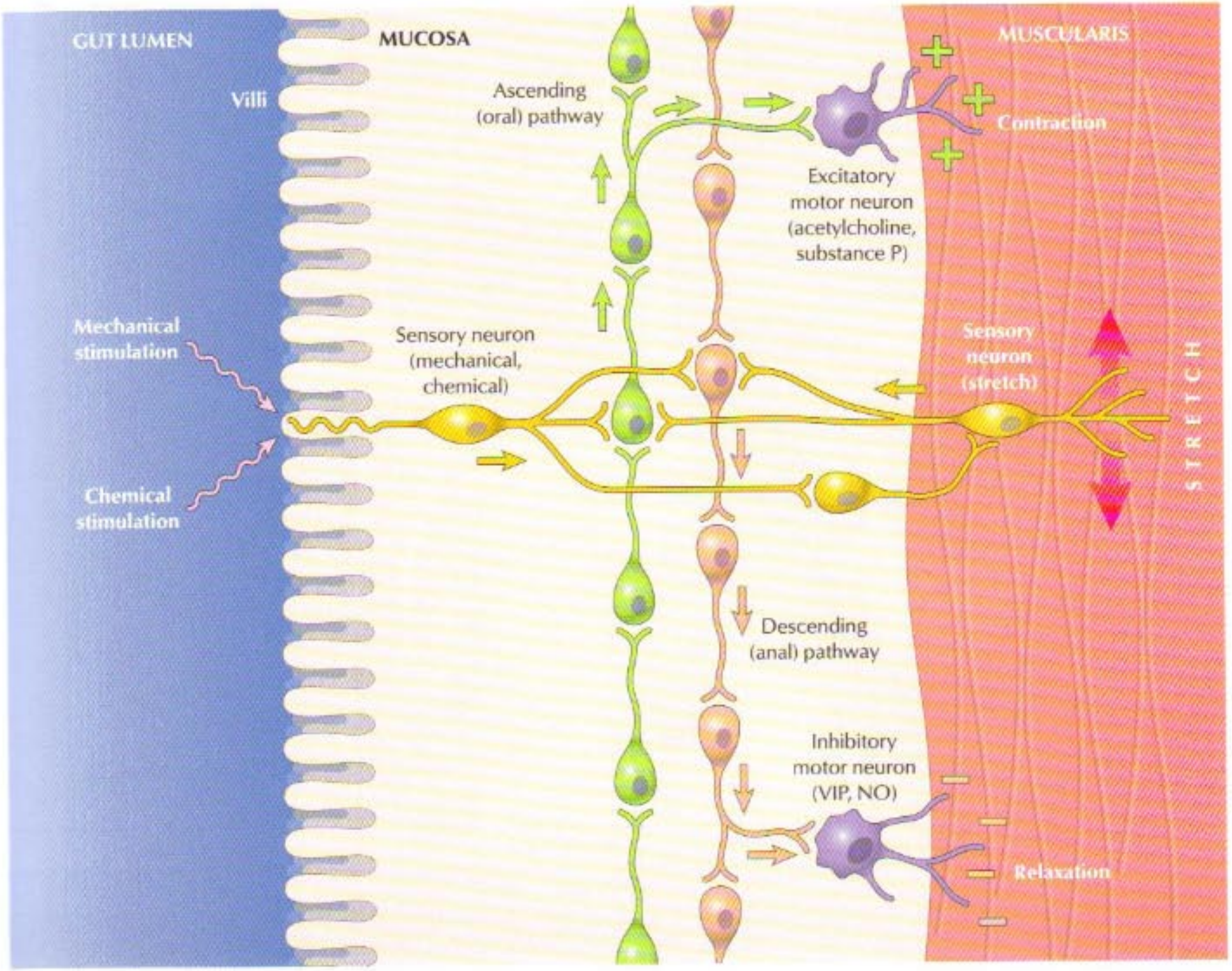
FIGURE 7.6 INTEGRATION OF AUTONOMIC AND ENTERIC NERVOUS SYSTEMS

This schematic summarizes the autonomic nervous system and enteric nervous system interconnections and coordination of gastric motility, secretion, and absorption. The autonomic nervous system, along with the cardiovascular, endocrine, and digestive systems, also regulate splanchnic blood flow both directly and via the enteric nervous system.


GUT LUMEN
Villi
MUCOSA
Ascending (oral) pathway
MUSCULARIS
Contraction
Excitatory motor neuron (acetylcholine, substance P)
Mechanical stimulation
Sensory neuron (mechanical, chemical)
Sensory neuron (stretch)
STRETCH
Chemical stimulation
Descending (anal) pathway
Inhibitory motor neuron (VIP, NO)
Relaxation

J. Perkins
MS, MFA
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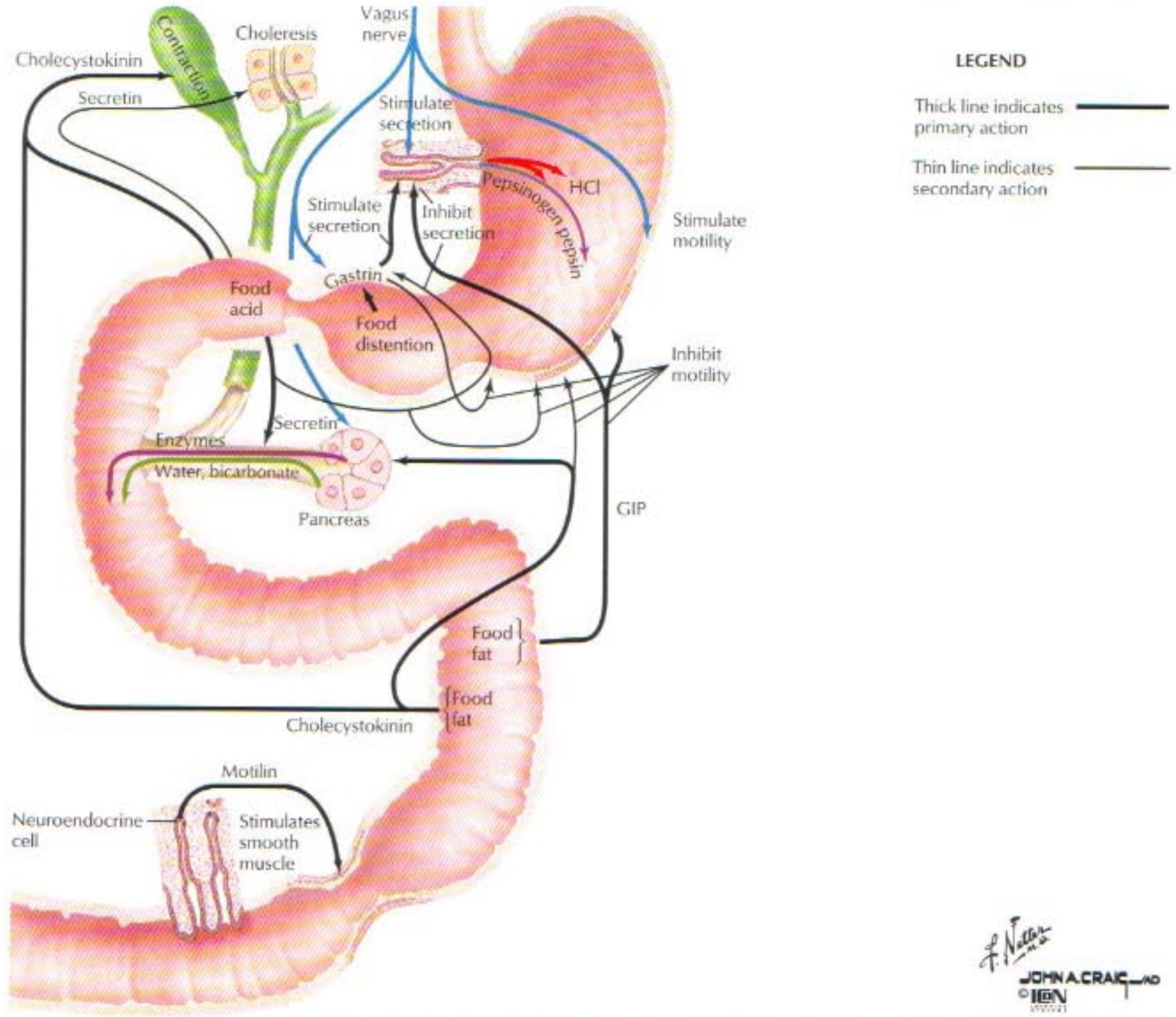
FIGURE 7.7 CONTROL OF PERISTALSIS

The presence of a bolus of food in the lumen of the intestine causes contraction of the smooth muscle above (green arrows) and relaxation below (peach arrows) the bolus. This process results in a peristaltic wave, which propels the bolus down the intestine (i.e., from the mouth toward the anus). This process is coordinated by the enteric nervous system. The neurons of the myenteric plexus depicted in this figure reside in the muscularis externa.


Cholecystokinin
Contraction
Choleresis
Secretin
Vagus nerve
Stimulate secretion
Stimulate secretion
Inhibit secretion
Pepsinogen
pepsin
HCl
Stimulate motility
LEGEND
Thick line indicates primary action
Thin line indicates secondary action
Food acid
Gastrin
Food distention
Inhibit motility
Secretin
Enzymes
Water, bicarbonate
Pancreas
GIP
Food fat
Food fat
Cholecystokinin
Motilin
Neuroendocrine cell
Stimulates smooth muscle
F. Netter M.D.
JOHN A. CRAIG MD
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Hormone	Neuroendocrine Cell Type and Location	Stimulus for Secretion	Primary Action	Other Actions
Gastrin	**G cell** Stomach, duodenum	Vagus, distention, amino acids	Stimulate HCl secretion	Inhibit gastric emptying
Secretin	**S cell** Duodenum	Acid	Stimulate pancreatic ductal cell H_2O and HCO_3^- secretion	Inhibit gastric secretion, inhibit gastric motility, and stimulate bile duct secretion of H_2O and HCO_3^-
Cholecystokinin	**I cell** Duodenum, jejunum	Fat, vagus	Stimulate enzyme secretion by pancreatic acinar cells and contract the gallbladder	Inhibit gastric motility
GIP*	**K cell** Duodenum, jejunum	Fat	Inhibit gastric secretion and motility	Stimulate insulin secretion
Motilin	**M cell** Duodenum, jejunum		Increased motility and initiates the MMC	

FIGURE 7.8 MAJOR GI HORMONES

The function of the GI tract is controlled by both neural (primarily parasympathetic fibers of the vagus nerve) and hormonal mechanisms. Five major GI hormones have been identified. In addition, a large number of other "candidate hormones," produced by neuroendocrine cells scattered through the mucosa of the stomach and intestines, also play a role in regulating and coordinating GI tract function (not listed). The primary, and some of the other secondary, actions of the five GI hormones are summarized. The "migrating motor (or myoelectric) complex" (MMC) occurs between meals with a period of 1 to 2 hours. It consists of a wave of peristalsis that serves to clean the GI tract by moving residual food particles distally.

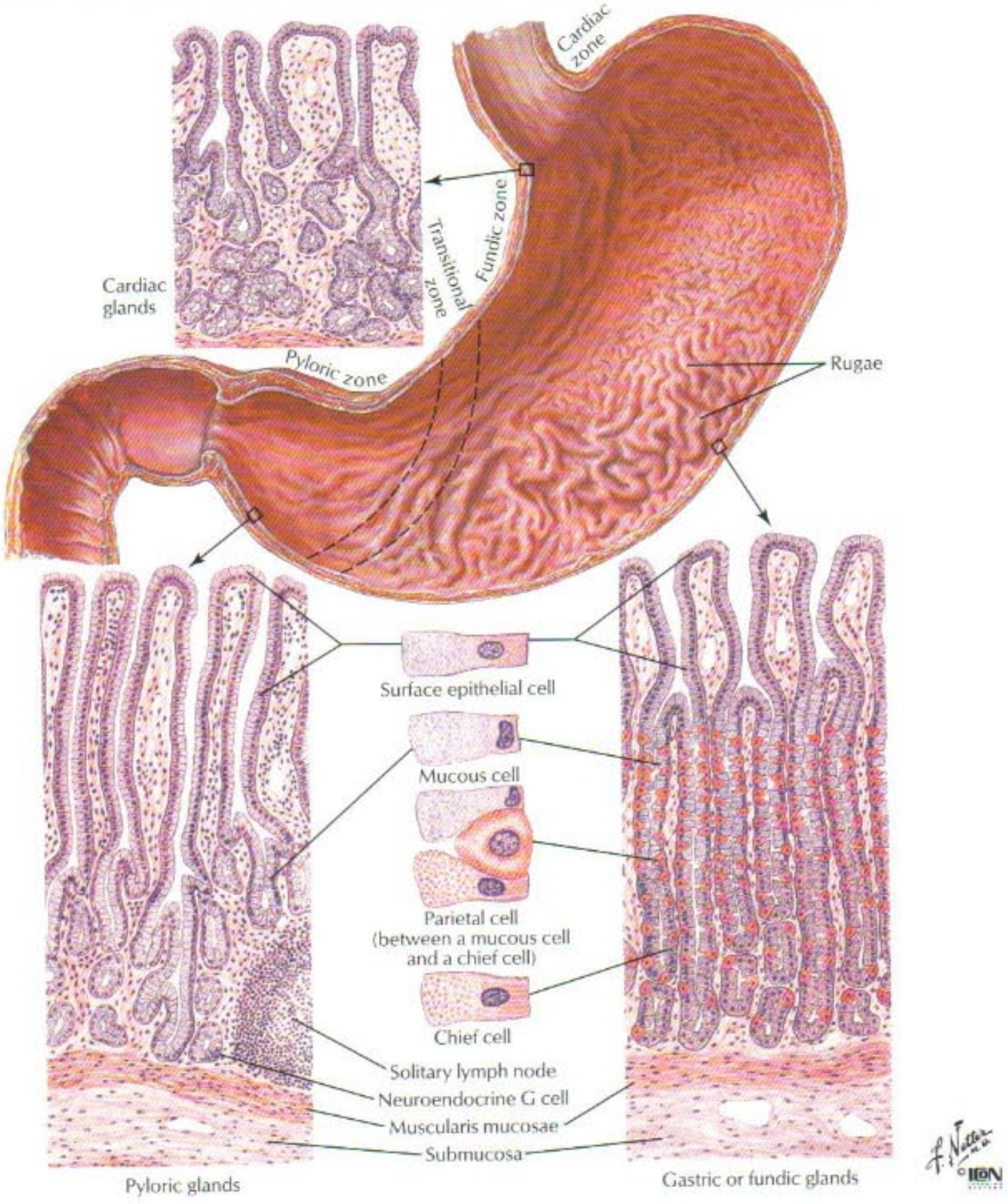
Cardiac zone
Fundic zone
Transitional zone
Cardiac glands
Pyloric zone
Rugae
Surface epithelial cell
Mucous cell
Parietal cell (between a mucous cell and a chief cell)
Chief cell
Solitary lymph node
Neuroendocrine G cell
Muscularis mucosae
Submucosa
Pyloric glands
Gastric or fundic glands
F. Netter M.D.
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FIGURE 7.9 STRUCTURE OF THE STOMACH

The surface of the stomach is thrown into numerous folds called rugae. The epithelium forms gastric pits with gastric glands at their base; these pits greatly increase the surface area for secretion. The glands differ in structure and cellular composition depending on their location. The cardiac glands are short and branched; the predominant cell type is the mucous cell. The mucous cells produce a watery (low-mucin) secretion that helps liquefy the gastric contents. The gastric or fundic glands are most numerous and form long, straight glands. In addition to mucous cells, they contain large numbers of parietal (HCl-secreting) cells and chief, or zymogen (pepsinogen-secreting), cells. The pyloric glands are branched and are composed mostly of mucous cells. Neuroendocrine cells (G cells) are found in the pyloric glands and are the cells that secrete gastrin. Surface epithelial cells are found in all regions of the stomach. They produce a thick (high-mucin) mucus, which serves to protect the surface cells of the stomach from abrasion by the ingested food.

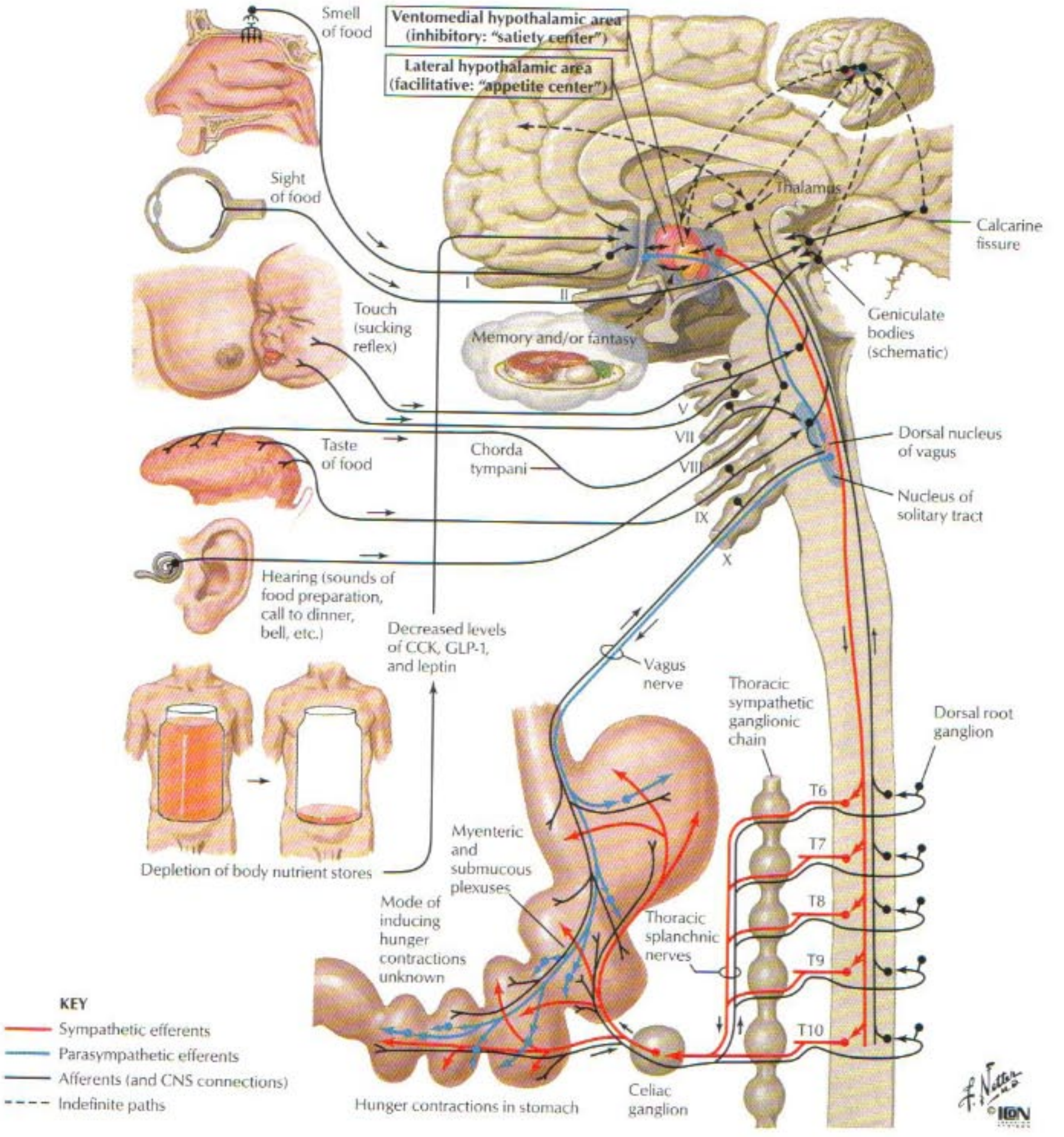
Smell of food
Ventomedial hypothalamic area (inhibitory: "satiety center")
Lateral hypothalamic area (facilitative: "appetite center")
Sight of food
Thalamus
Calcarine fissure
I
II
Touch (sucking reflex)
Memory and/or fantasy
Geniculate bodies (schematic)
V
VII
VIII
IX
X
Taste of food
Chorda tympani
Dorsal nucleus of vagus
Nucleus of solitary tract
Hearing (sounds of food preparation, call to dinner, bell, etc.)
Decreased levels of CCK, GLP-1, and leptin
Vagus nerve
Thoracic sympathetic ganglionic chain
Dorsal root ganglion
T6
T7
T8
T9
T10
Myenteric and submucous plexuses
Depletion of body nutrient stores
Mode of inducing hunger contractions unknown
Thoracic splanchnic nerves
KEY
Sympathetic efferents
Parasympathetic efferents
Afferents (and CNS connections)
Indefinite paths
Hunger contractions in stomach
Celiac ganglion
F. Netter M.D.
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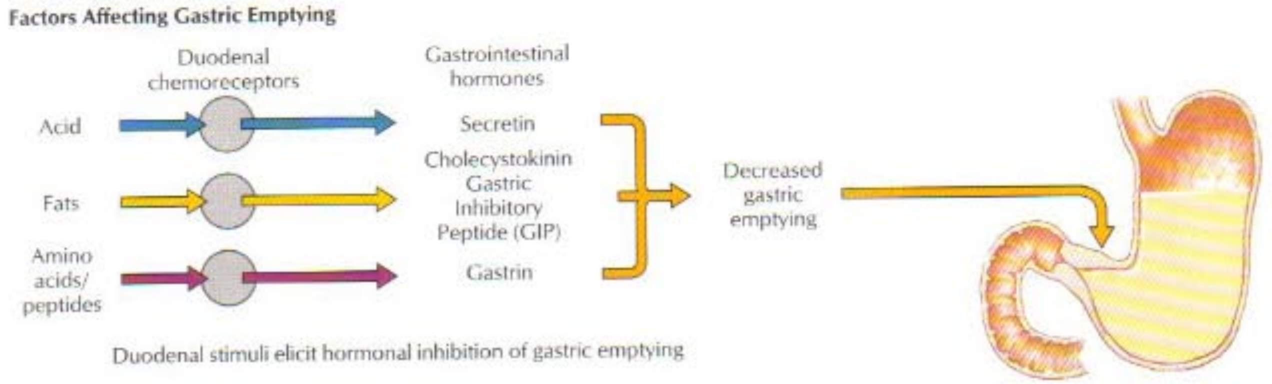
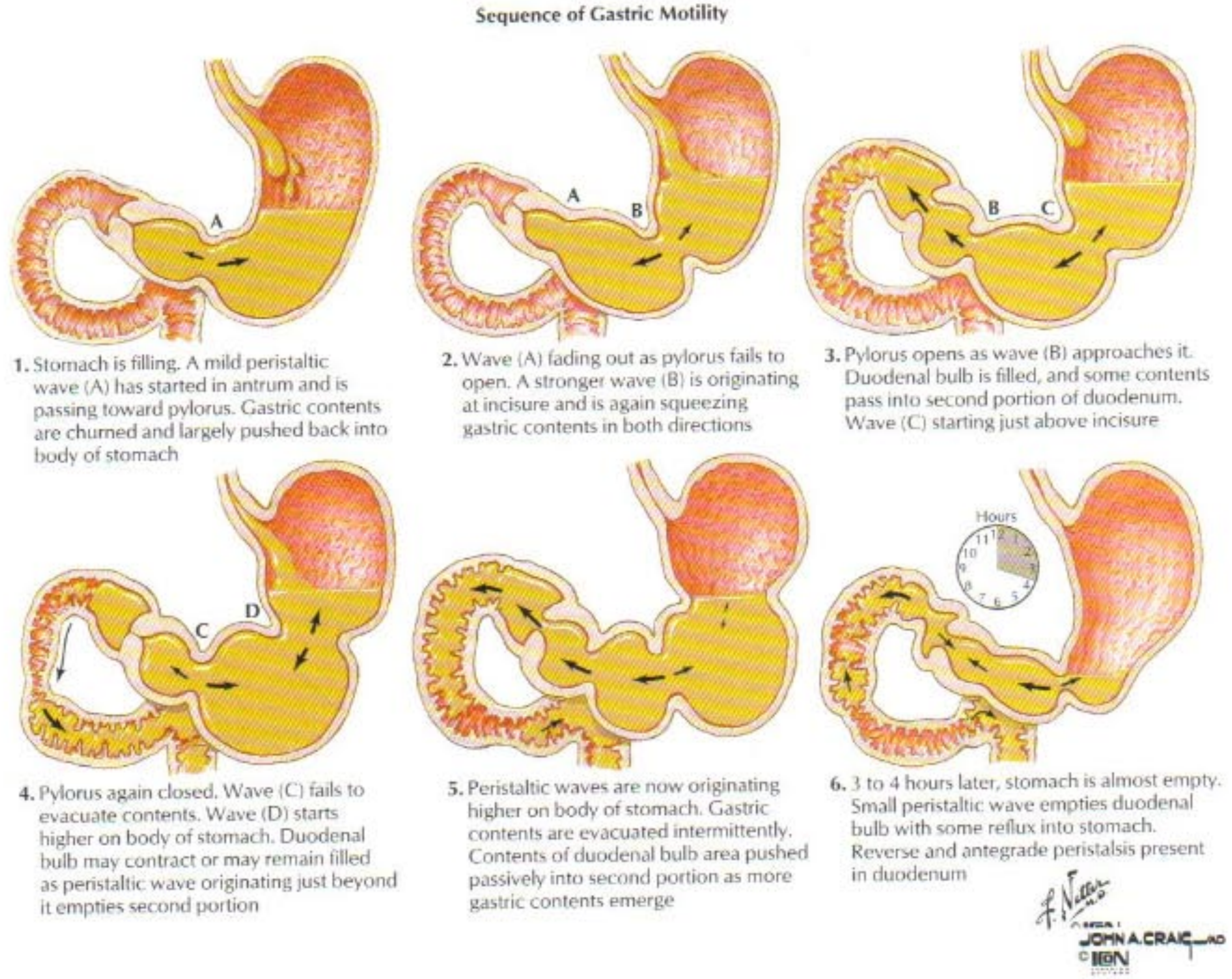
FIGURE 7.10 APPETITE AND HUNGER

The sensations of hunger and satiety are complex and include multiple neural pathways, as well as circulating hormones. Depicted here are pathways involved in the sensation of hunger. Although our understanding is incomplete, the hypothalamus is known to play a critical role in controlling appetite and food intake. When food is ingested, cholecystokinin and GLP-1 (glucagon-like peptide) are released from neuroendocrine cells in the intestine. These hormones suppress appetite and give the sensation of satiety. In the absence of food, the levels of these hormones are low. Long-term regulation of food intake may involve the hormone leptin, which is produced by fat cells. When fat stores are high, leptin is released and thought to act on the hypothalamus to suppress appetite. When body nutrient stores are depleted, leptin levels are low.


Factors Affecting Gastric Emptying
Duodenal chemoreceptors
Gastrointestinal hormones
Acid
Secretin
Fats
Cholecystokinin
Gastric Inhibitory Peptide (GIP)
Amino acids/ peptides
Gastrin
Decreased gastric emptying

Duodenal stimuli elicit hormonal inhibition of gastric emptying


Sequence of Gastric Motility
A
A
B
B
C
C
D
Hours
F. Netter
JOHN A. CRAIG AD
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1. Stomach is filling. A mild peristaltic wave (A) has started in antrum and is passing toward pylorus. Gastric contents are churned and largely pushed back into body of stomach
2. Wave (A) fading out as pylorus fails to open. A stronger wave (B) is originating at incisure and is again squeezing gastric contents in both directions
3. Pylorus opens as wave (B) approaches it. Duodenal bulb is filled, and some contents pass into second portion of duodenum. Wave (C) starting just above incisure
4. Pylorus again closed. Wave (C) fails to evacuate contents. Wave (D) starts higher on body of stomach. Duodenal bulb may contract or may remain filled as peristaltic wave originating just beyond it empties second portion
5. Peristaltic waves are now originating higher on body of stomach. Gastric contents are evacuated intermittently. Contents of duodenal bulb area pushed passively into second portion as more gastric contents emerge
6. 3 to 4 hours later, stomach is almost empty. Small peristaltic wave empties duodenal bulb with some reflux into stomach. Reverse and antegrade peristalsis present in duodenum

FIGURE 7.11 GASTRIC MOTILITY

The motility of the stomach is under neural and hormonal control. As food is swallowed, vagal efferents release vasoactive intestinal peptide (VIP) to relax the stomach. Mixing and churning of the food (chyme) results from contractions beginning in the middle of the stomach and traveling toward the pylorus. Over time, small amounts of chyme are ejected into the duodenum with each contraction wave. The emptying of the stomach varies with the nature of the contents of the food. For example, the rate of empting is starch > protein > fat. Also, solid foods empty slower than liquids. The emptying of the stomach is also controlled by hormones released by neuroendocrine cells in the duodenum and jejunum. These cells monitor the intestinal contents and then modulate the rate of gastric emptying (upper panel).

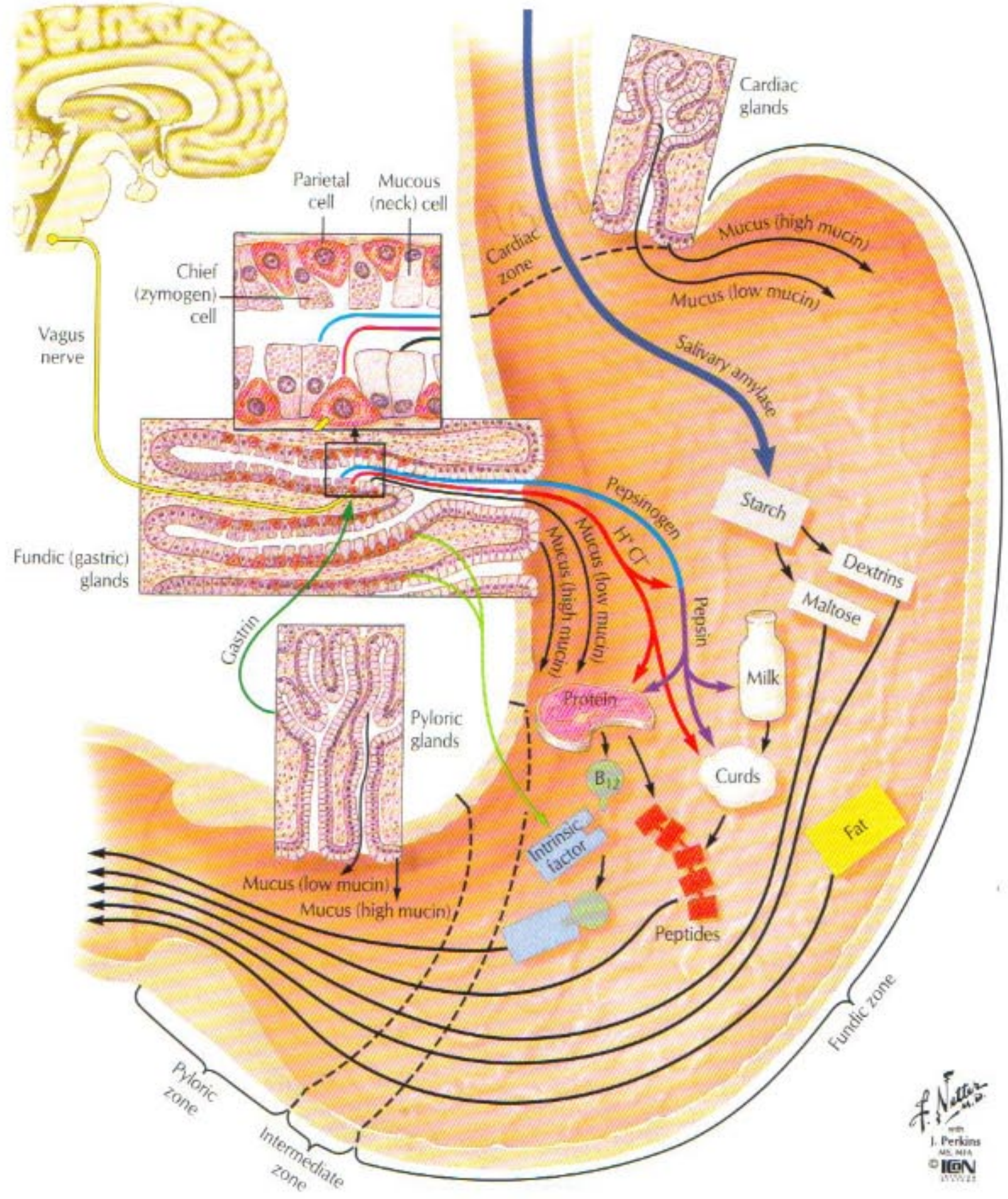
Parietal cell
Mucous (neck) cell
Chief (zymogen) cell
Vagus nerve
Fundic (gastric) glands
Gastrin
Pyloric glands
Mucus (low mucin)
Mucus (high mucin)
Cardiac glands
Cardiac zone
Mucus (high mucin)
Mucus (low mucin)
Salivary amylase
Starch
Dextrins
Maltose
Pepsinogen
H^+Cl^-
Mucus (low mucin)
Mucus (high mucin)
Pepsin
Milk
Protein
Curds
B_{12}
Intrinsic factor
Peptides
Fat
Pyloric zone
Intermediate zone
Fundic zone
F. Netter M.D.
with J. Perkins MS, MFA
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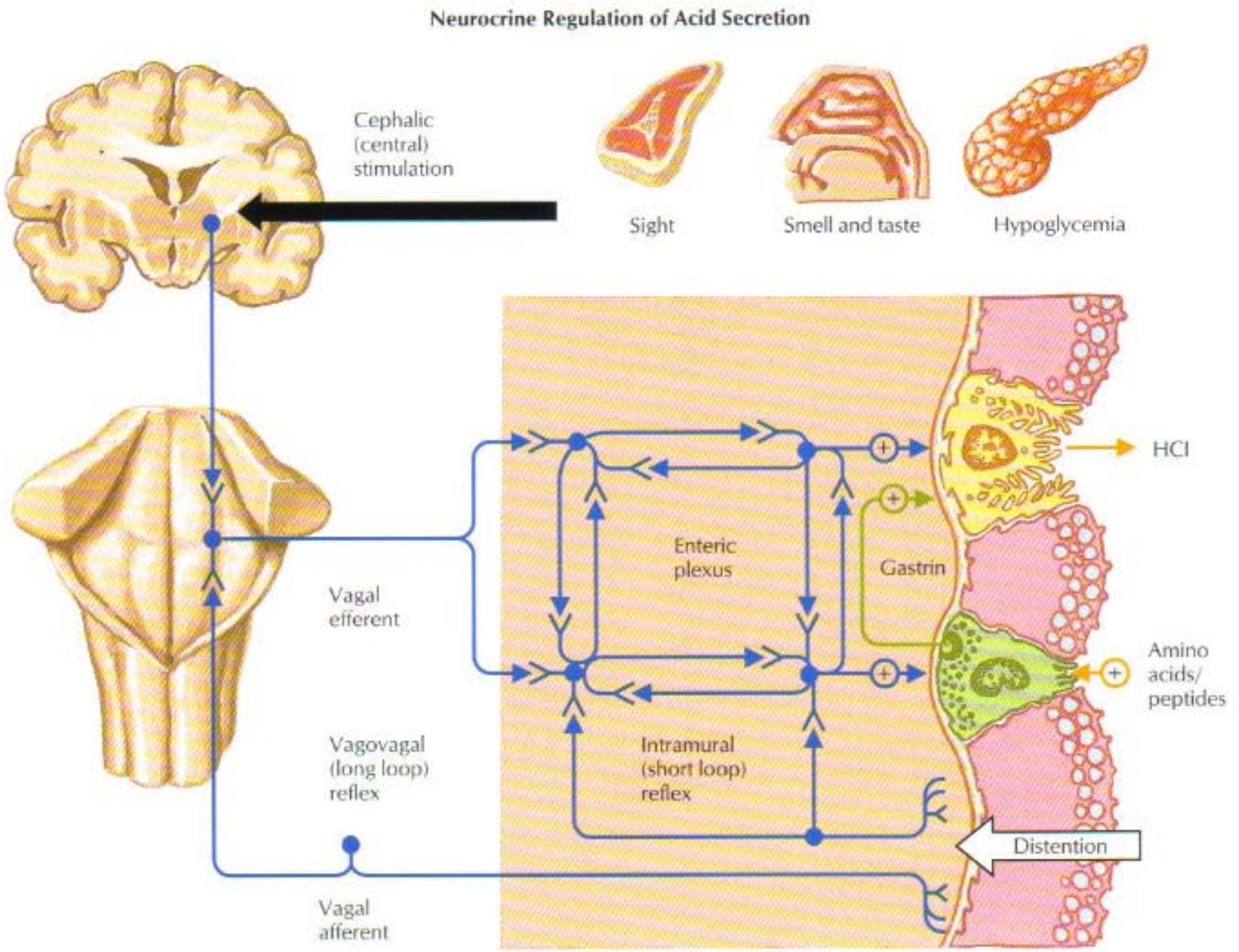
FIGURE 7.12 GASTRIC DIGESTIVE FUNCTION

The stomach serves to break food in to small, more easily digestible fragments. In addition, it begins the enzymatic digestion of proteins through the action of pepsin and HCl. Ingested starches continue to be broken down by salivary amylase. Some fat digestion begins in the mouth and stomach mediated by the presence of lingual and gastric lipase (not shown in figure). The parietal cells also secrete intrinsic factor, which complexes vitamin B_{12}. Absorption of B_{12} then occurs in the terminal portion of the ileum.


Neurocrine Regulation of Acid Secretion

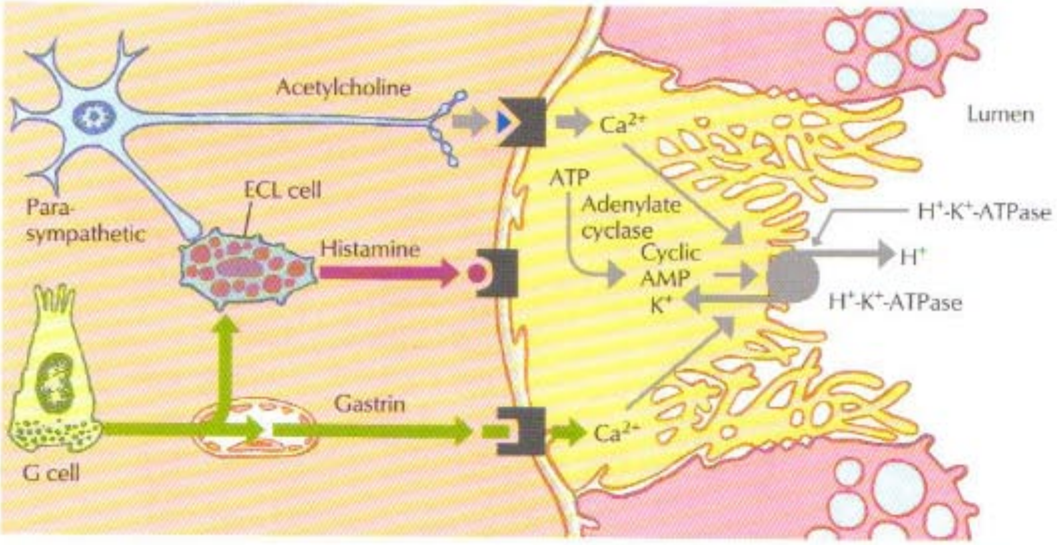
Cephalic
(central)
stimulation
Sight
Smell and taste
Hypoglycemia
HCl
Enteric
plexus
Gastrin
Vagal
efferent
Amino
acids/
peptides
Vagovagal
(long loop)
reflex
Intramural
(short loop)
reflex
Distention
Vagal
afferent

Gastric acid secretion initiated and modulated by nervous system via central stimulation through vagal efferents and enteric plexus and by intramural (short) feedback loop and a second (long, or vagovagal) feedback loop, both stimulated by gastric antral distention

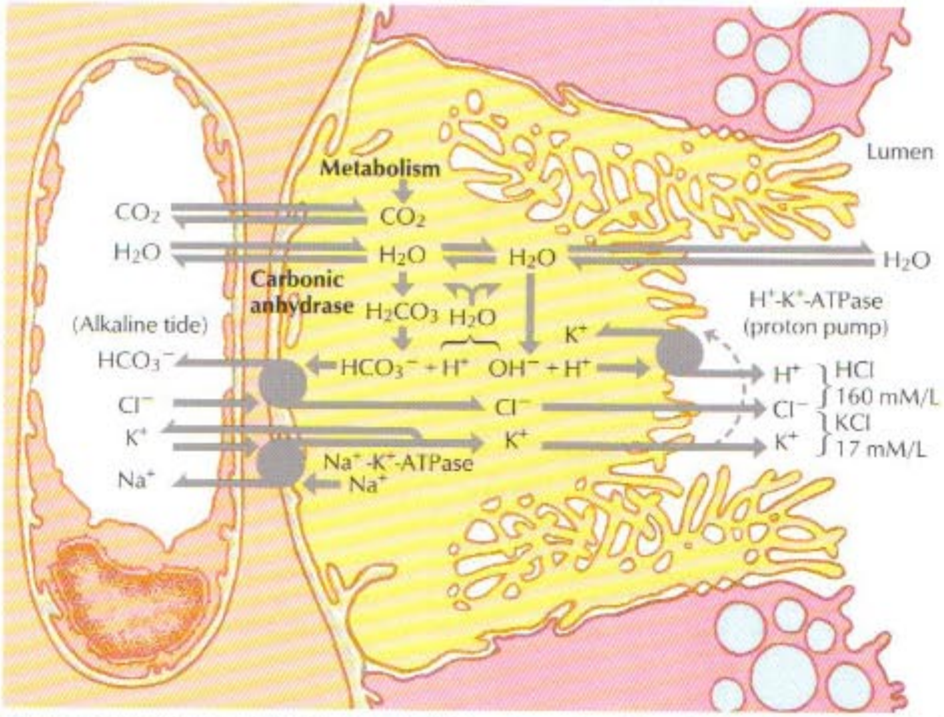
JOHN A.CRAIG_AD
©ICON

FIGURE 7.13 VAGAL CONTROL OF GASTRIC SECRETION

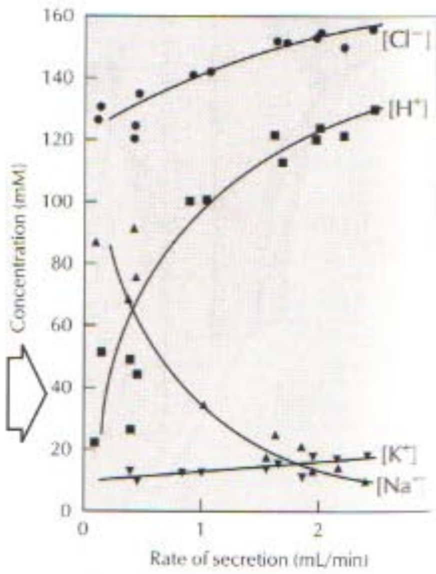
Gastric secretion, in response to sight, smell, taste, and chewing of food, is initiated and modulated by the vagus nerves of the autonomic nervous system. This initial stimulation of secretomotor activity is referred to as the "cephalic phase." The vagal stimulation acts via the enteric nervous system to initiate gastric secretion of acid (HCl) and gastrin. The presence of acid, amino acids, and peptides, as well as gastric distention, effectively stimulates the next phase of gastric secretion, termed the "gastric phase."


Acetylcholine
Ca^{2+}
Lumen
Para-sympathetic
ECL cell
ATP
Adenylate cyclase
H$^+$-K$^+$-ATPase
Histamine
Cyclic AMP
K$^+$
H$^+$
H$^+$-K$^+$-ATPase
Gastrin
Ca^{2+}
G cell

Secretions of gastric acid (H$^+$) by parietal cell mediated by neurocrine, paracrine, and endocrine mechanisms. Medical or surgical blockade of these mechanisms affords therapeutic options


Metabolism
Lumen
CO$_2$
CO$_2$
H$_2$O
H$_2$O
H$_2$O
H$_2$O
Carbonic anhydrase
H$_2$CO$_3$
H$_2$O
H$^+$-K$^+$-ATPase (proton pump)
(Alkaline tide)
K$^+$
HCO$_3^-$
HCO$_3^-$ + H$^+$
OH$^-$ + H$^+$
H$^+$
HCl 160 mM/L
Cl$^-$
Cl$^-$
Cl$^-$
KCl 17 mM/L
K$^+$
K$^+$
K$^+$
Na$^+$-K$^+$-ATPase
Na$^+$
Na$^+$

Parietal cell mechanisms of acid (H$^+$) secretion involve series of chemical exchanges across basal membrane, with final active exchange of H$^+$ for K$^+$ mediated across apical (secretory) membrane by H$^+$-K$^+$-ATPase (proton pump)

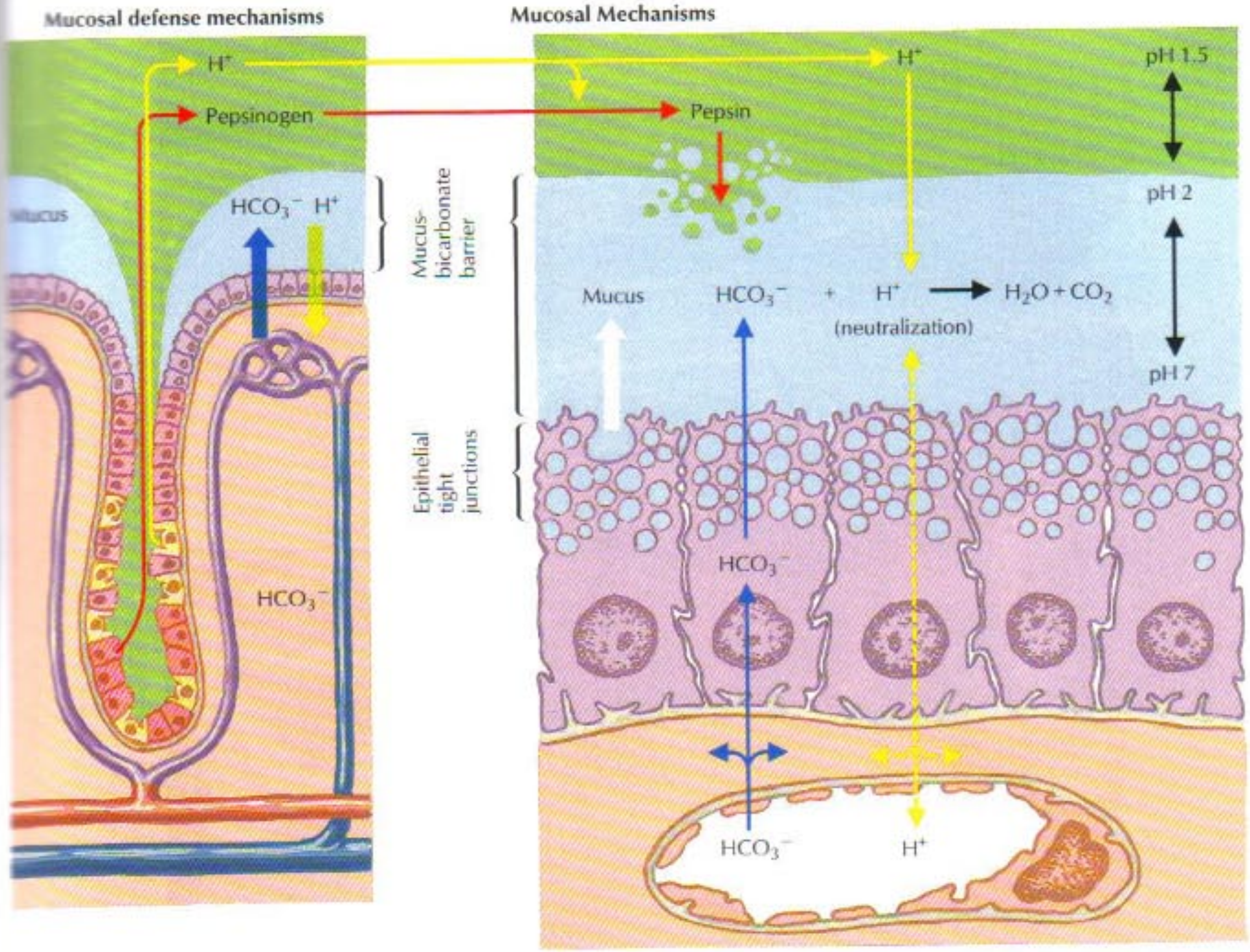


Gastric fluid ion concentration as a function of gastric secretion rate

JOHN A.CRAIG

FIGURE 7.14 REGULATION OF PARIETAL CELL FUNCTION

The parietal cells secretes HCl via an H$^+$-K$^+$-ATPase (H$^+$ pump). Carbonic anhydrase within the parietal cells catalyzes the hydration of CO$_2$ and ultimately the production of H$^+$. The parietal cell is stimulated to secrete HCl by vagal efferent fibers (parasympathetic), gastrin, and histamine. Gastrin is produced and released from neuroendocrine G cells. The enterochromaffin-like cells (ECL cells) release histamine, which acts synergistically with acetylcholine and gastrin t stimulate secretion. Somatostatin produced by neuroendocrine D cells (not shown) acts on the G cell to inhibit gastrin release.


Mucosal defense mechanisms
Mucosal Mechanisms
H^+
Pepsinogen
Mucus
HCO_3^- H^+
Mucus-bicarbonate barrier
Epithelial tight junctions
HCO_3^-
H^+
Pepsin
pH 1.5
pH 2
pH 7
Mucus
HCO_3^- + H^+ → $H_2O + CO_2$
(neutralization)
HCO_3^-
HCO_3^-
H^+

Gastric mucosa and submucosa protected from chemical injury by mucus-bicarbonate surface barrier that neutralizes gastric H^+ and by epithelial "tight junctions" that prevent H^+ access to subepithelial tissue

JOHN A.CRAIG AD
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FIGURE 7.15 MUCOSAL DEFENSE MECHANISMS

The high-mucin-containing mucus produced by the surface epithelial cells protects the stomach from abrasion and provides a relatively alkaline environment for the epithelial cells. This mucus layer traps bicarbonate and remains relatively stable, providing a pH of 7.0 just above the surface epithelium, compared to a pH of 1.5 in the gastric lumen.

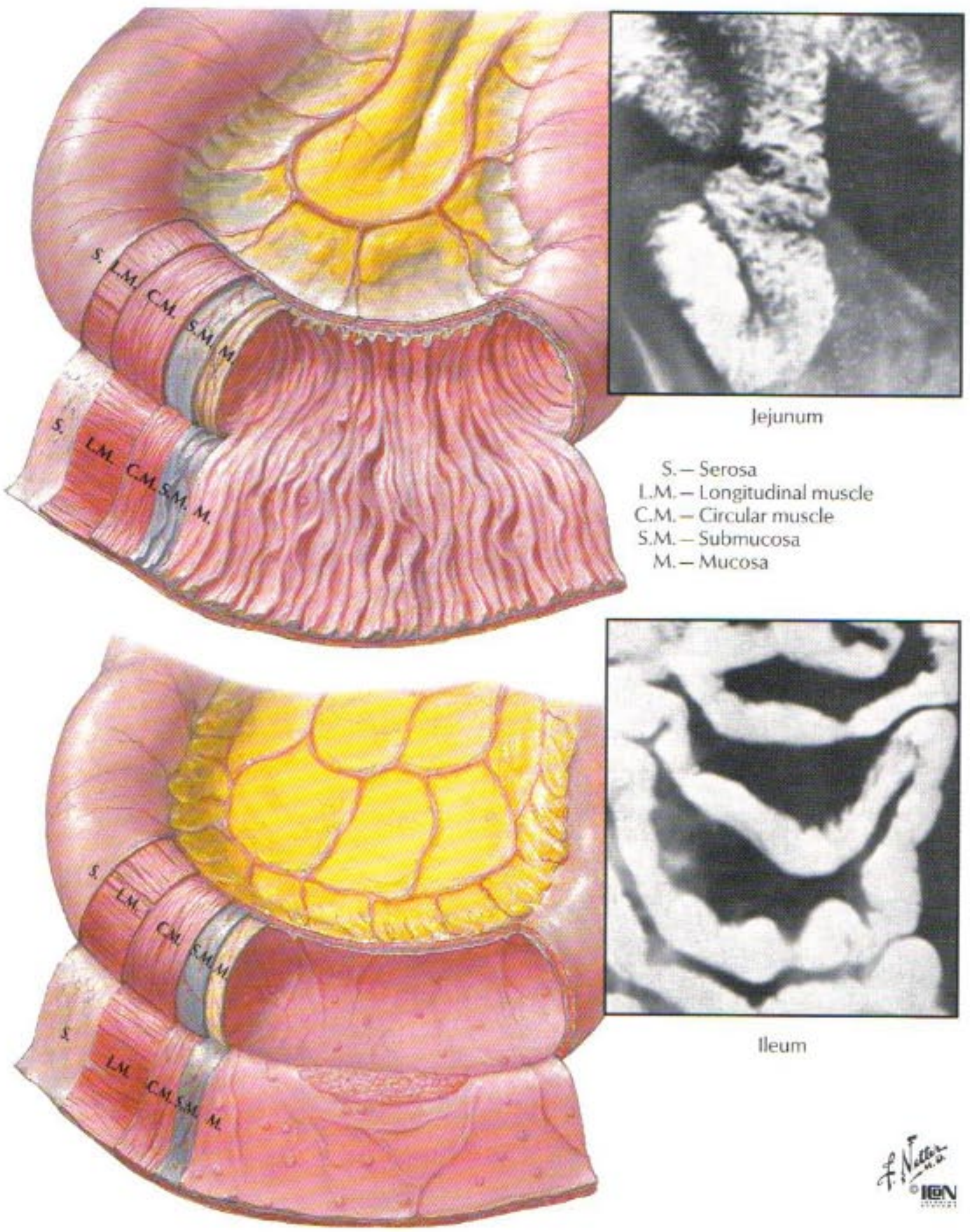
S.
L.M.
C.M.
S.M.
M.
Jejunum
S. — Serosa
L.M. — Longitudinal muscle
C.M. — Circular muscle
S.M. — Submucosa
M. — Mucosa
Ileum
F. Netter M.D.
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FIGURE 7.16 SMALL INTESTINE STRUCTURE

The duodenum, jejunum, and ileum comprise the small intestine. Anatomically, the duodenum is the shortest segment (about 25 cm long), while the jejunum and ileum are about 6-7 meters long, with the jejunum accounting for the proximal two-fifths of this length. Compared with the ileum, the jejunum has a larger diameter, thicker walls, greater vascularity, less mesenteric fat, fewer lymph nodules, and larger and taller circular mucosal folds (plicae circulares). The absorptive surface is larger in the jejunum as evident in the barium-contrast x-rays of each segment.

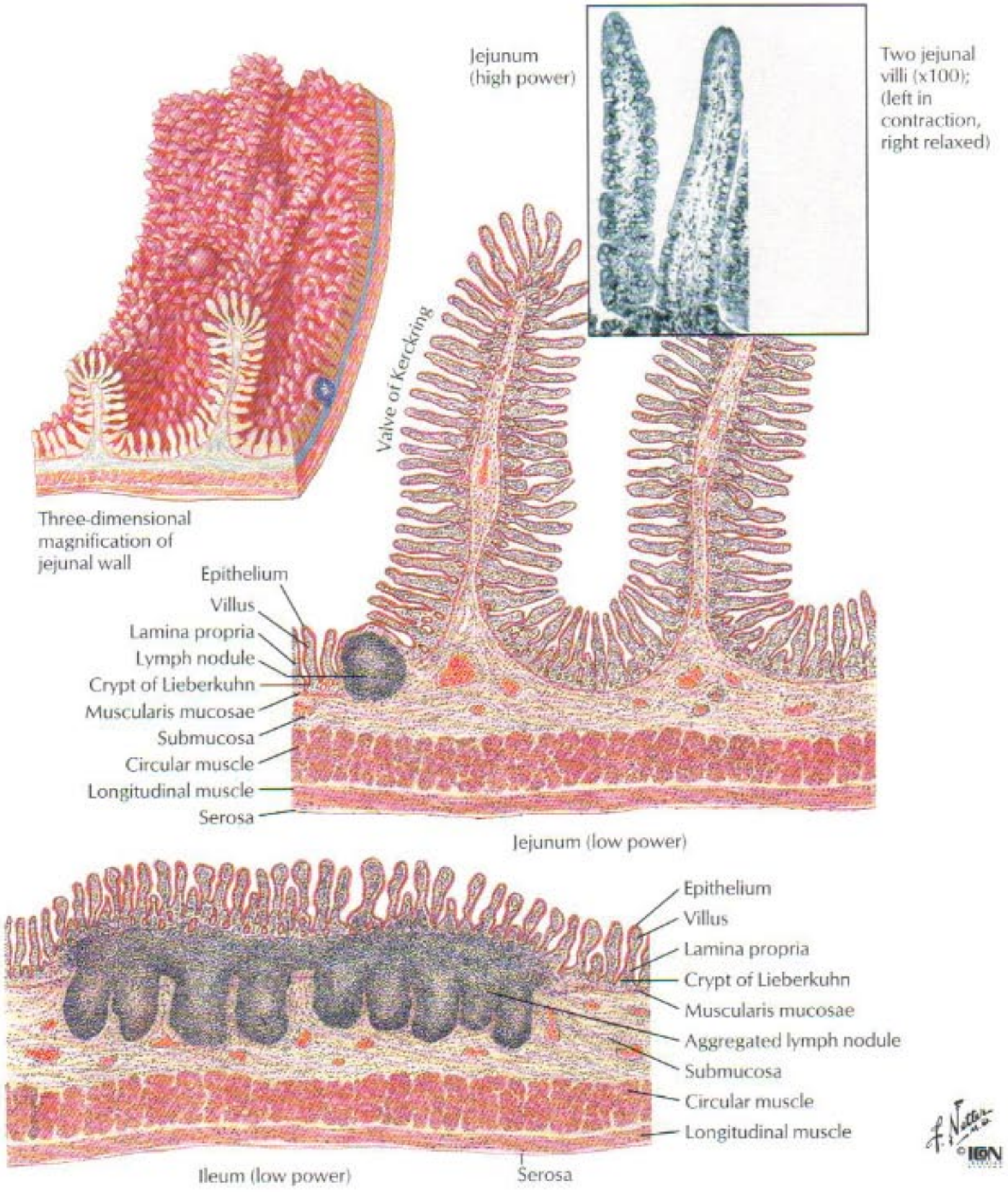
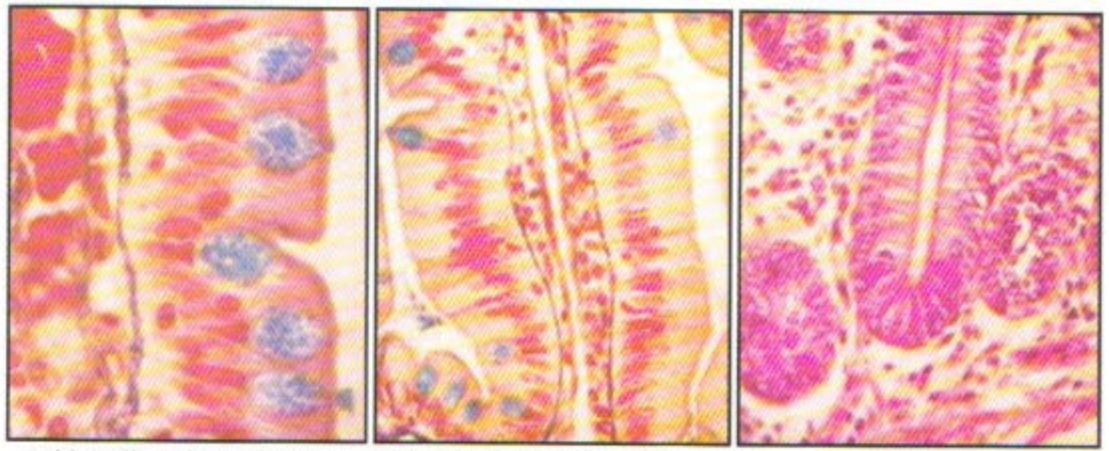

Jejunum (high power)
Two jejunal villi (x100); (left in contraction, right relaxed)
Valve of Kerckring
Three-dimensional magnification of jejunal wall
Epithelium
Villus
Lamina propria
Lymph nodule
Crypt of Lieberkuhn
Muscularis mucosae
Submucosa
Circular muscle
Longitudinal muscle
Serosa
Jejunum (low power)
Epithelium
Villus
Lamina propria
Crypt of Lieberkuhn
Muscularis mucosae
Aggregated lymph nodule
Submucosa
Circular muscle
Longitudinal muscle
Ileum (low power)
Serosa

FIGURE 7.17 **SMALL INTESTINE MICROSCOPIC STRUCTURE**

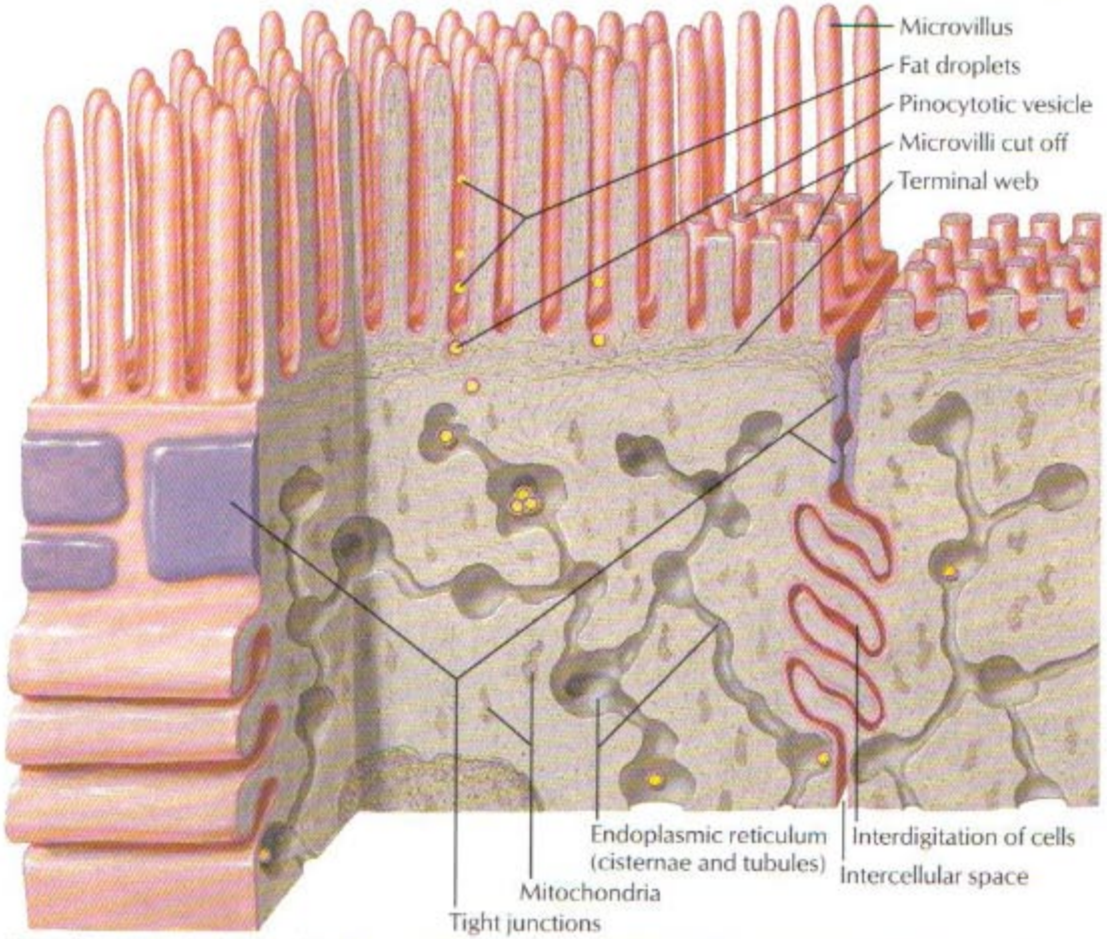
The jejunum and ileum have a large surface area for secretion and absorption. The surface area is increased by presence of circular folds (valves or rings of Kerckring), villi, and microvilli. Because the small intestine provides a large surface interface between the external and internal environments, it represents a first-line defense against foreign antigens. Accordingly, large collections of lymphoid tissue are found in the lamina propria and submucosa. In general, the following changes occur from the proximal jejunum to the terminal ileum; the number and length of the villi decrease, the number of mucous cells increases, and there is an increase in the amount of lymphoid tissue.



Goblet cells and striated border of human jejunal villus (azan stain, ×650)

Central lacteal (chyliferous vessel) in human jejunal villus (azan stain, ×325)

Floor of crypt of Lieberkühn with granulated, oxyphilic cells of Paneth (hematoxylin-eosin, ×325)


Microvillus
Fat droplets
Pinocytotic vesicle
Microvilli cut off
Terminal web
Endoplasmic reticulum (cisternae and tubules)
Interdigitation of cells
Intercellular space
Mitochondria
Tight junctions

Three-dimensional schema of striated border of intestinal epithelial cells (based on ultramicroscopic studies)

FIGURE 7.18 EPITHELIUM OF THE SMALL INTESTINE

The villi are lined with a single layer of columnar epithelial cells called enterocytes. The apical membrane of the enterocytes contains numerous microvilli. The enterocytes are involved in absorption of nutrients and the secretion of fluid into the intestinal lumen. Interspersed among the enterocytes are goblet cells, which secrete mucus. The crypts of Lieberkuhn are located at the base of the vill and are the site where actively dividing cells are found. The newly formed cells migrate up the villus over the course of 3 to 5 days an are sloughed into the lumen. The crypts also contain Paneth cells, which secrete the antibacterial enzyme lysozyme.

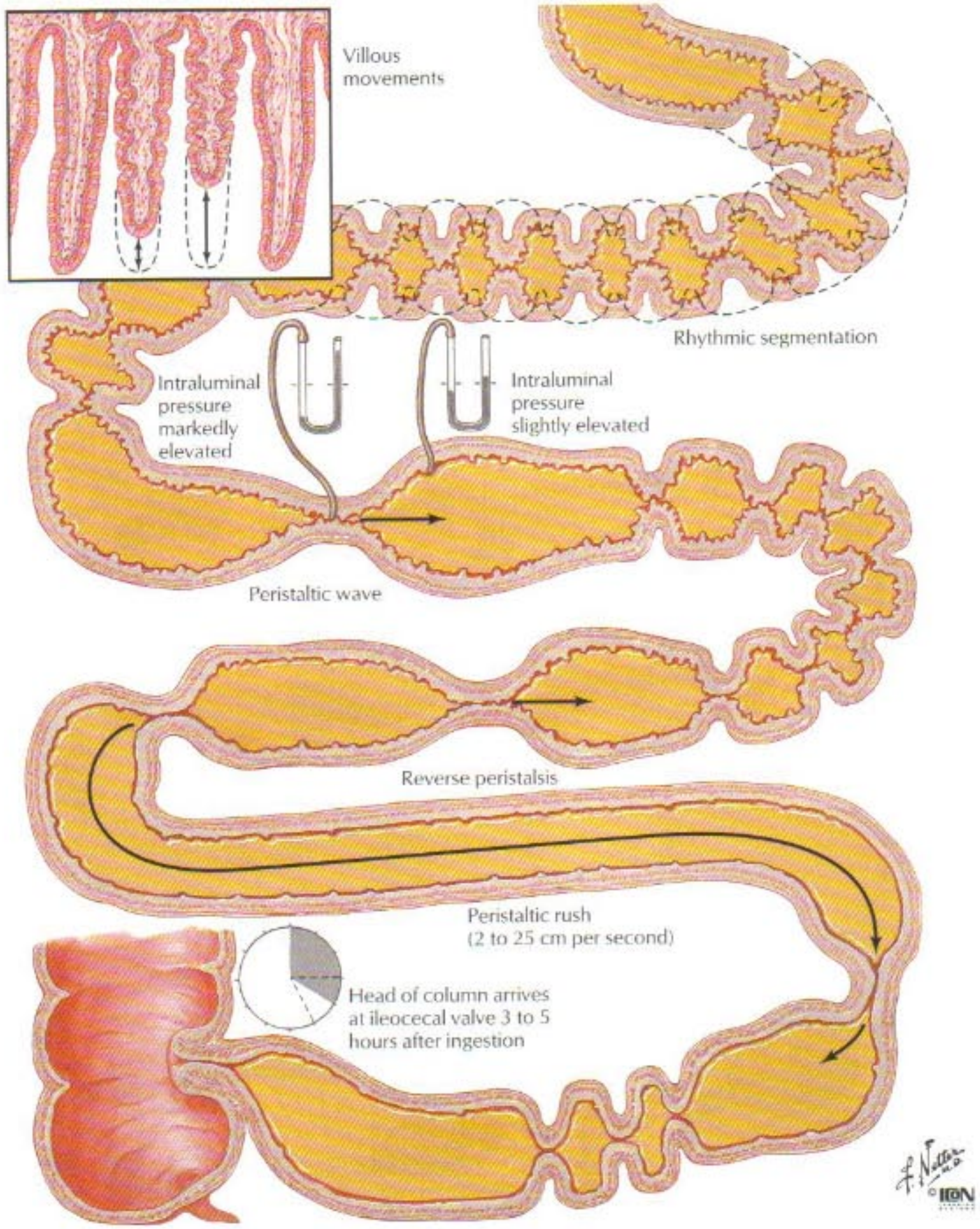
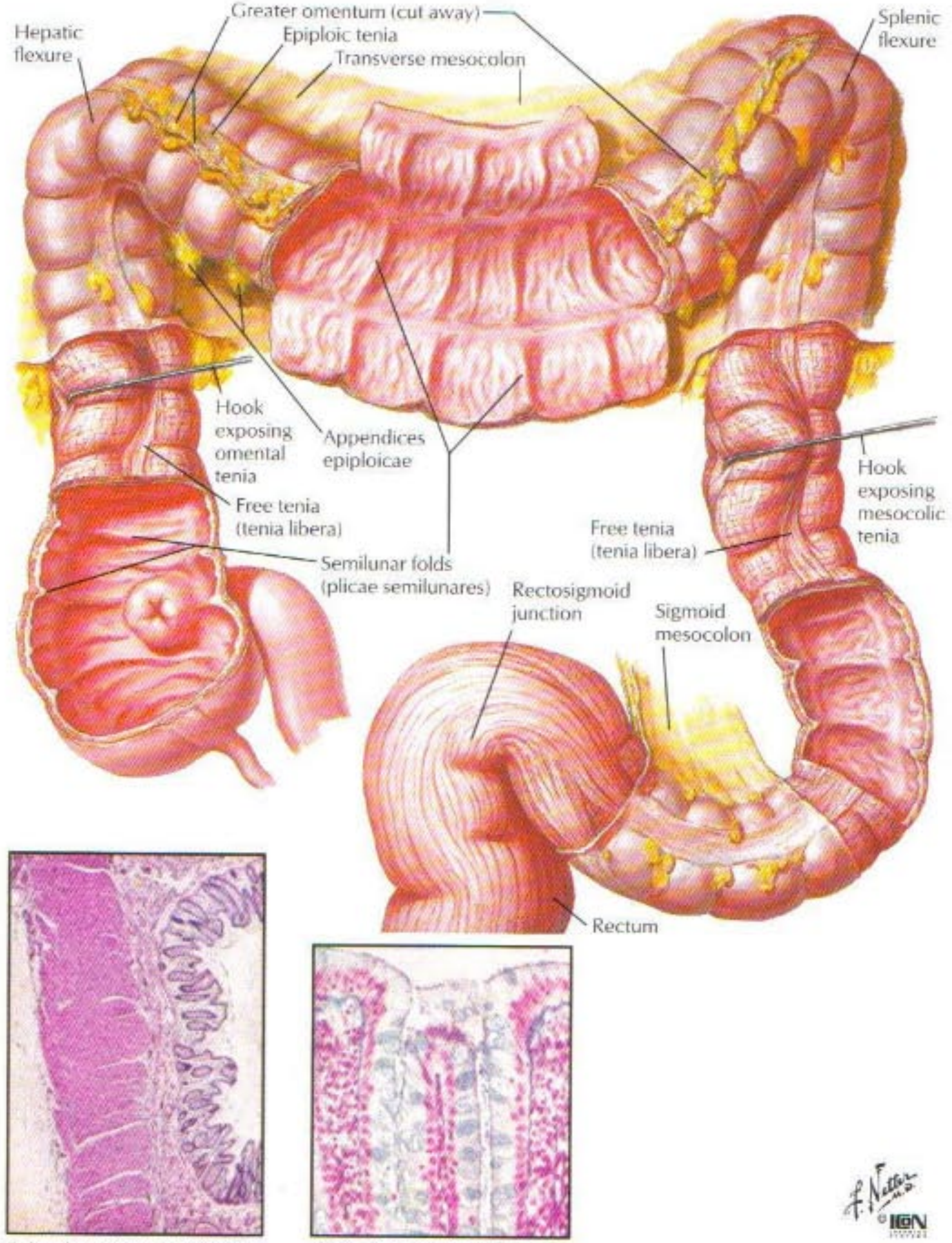

Villous movements
Rhythmic segmentation
Intraluminal pressure markedly elevated
Intraluminal pressure slightly elevated
Peristaltic wave
Reverse peristalsis
Peristaltic rush (2 to 25 cm per second)
Head of column arrives at ileocecal valve 3 to 5 hours after ingestion

FIGURE 7.19 MOTILITY OF THE SMALL INTESTINE

The small intestine has two general types of motility patterns. These motility patterns are under the control of the enteric nervous system (primarily the myenteric plexus). The first pattern, segmentation, serves to mix and churn the luminal contents. The second pattern, peristalsis, serves to move the luminal contents distally. In some instances, reverse peristalsis occurs, as does a peristaltic rush. In the absence of food (interdigestive phase), there is a periodic wave (every 1 to 2 hours) of peristalsis that begins in the stomach and sweeps down the length of the small intestine. This wave is called the migrating motor (or myoelectric) complex (MMC) and serves to clean the intestine and maintain a low bacterial count in the small intestine. The MMC is modulated by motilin.


Greater omentum (cut away)
Hepatic flexure
Epiploic tenia
Transverse mesocolon
Splenic flexure
Hook exposing omental tenia
Appendices epiploicae
Free tenia (tenia libera)
Semilunar folds (plicae semilunares)
Free tenia (tenia libera)
Hook exposing mesocolic tenia
Rectosigmoid junction
Sigmoid mesocolon
Rectum
F. Netter
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Colon: low-power longitudinal section through entire wall

Colonic mucosa; goblet cells in crypts (azan stain, ×160)

FIGURE 7.20 LARGE INTESTINE STRUCTURE

The large intestine serves primarily to reabsorb water and electrolytes from the feces and to store the feces until they are eliminated from the body. The large intestine consists of the cecum, appendix, colon, rectum, and anal canal. Like the small intestine, the large intestine has two smooth muscle layers, but the outer longitudinal muscle is organized into three thickened bands (teniae coli) that run from the cecum to the rectum. The colon is subdivided into a retroperitoneal ascending colon, a transverse colon tethered by a mesentery, a retroperitoneal descending colon, and a mesenteric sigmoid colon. A large number of mucus-producing goblet cells are found in the colon. They produce a copious amount of mucus for lubrication.

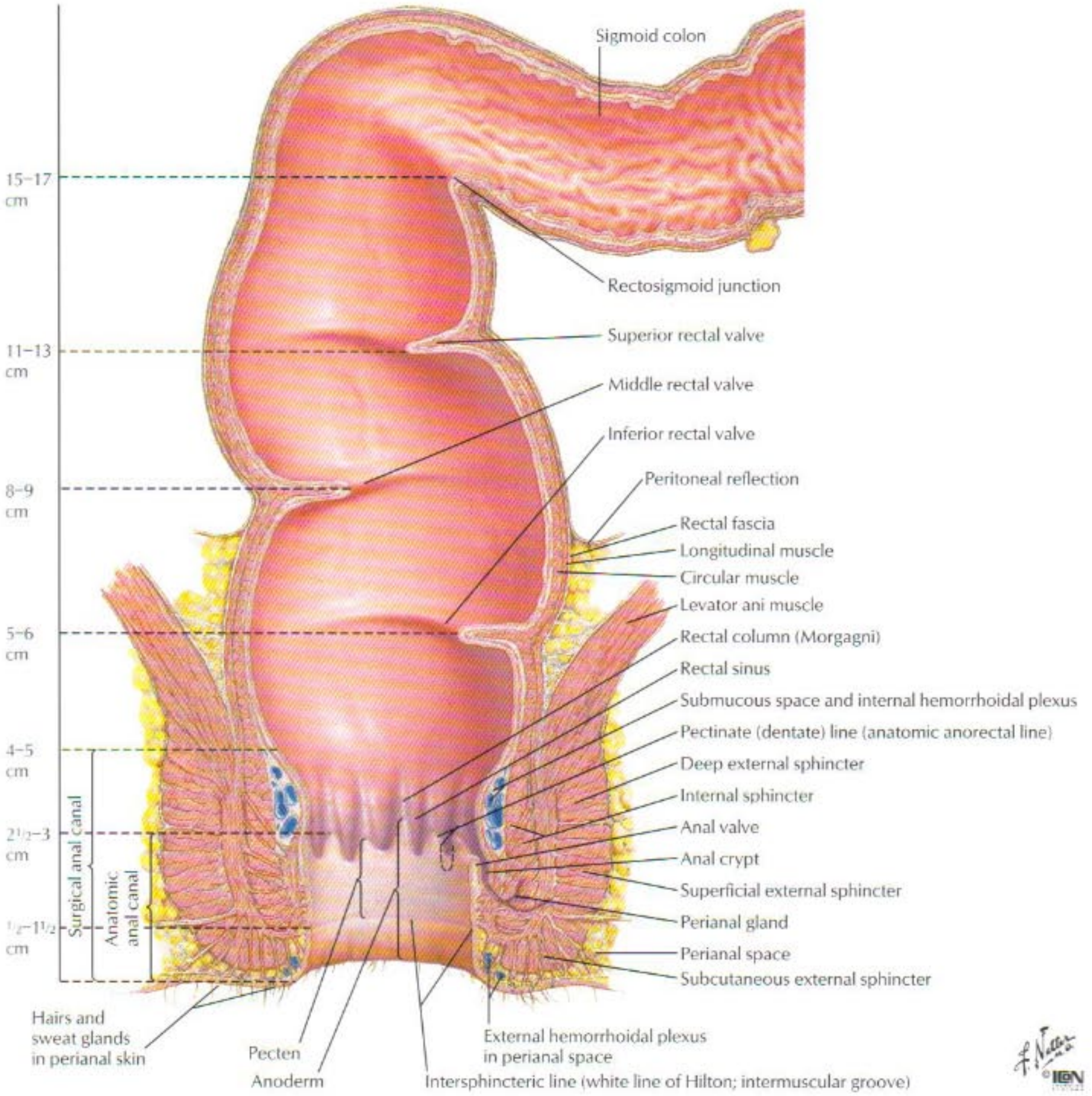
Sigmoid colon
15–17 cm
Rectosigmoid junction
Superior rectal valve
11–13 cm
Middle rectal valve
Inferior rectal valve
8–9 cm
Peritoneal reflection
Rectal fascia
Longitudinal muscle
Circular muscle
Levator ani muscle
5–6 cm
Rectal column (Morgagni)
Rectal sinus
Submucous space and internal hemorrhoidal plexus
Pectinate (dentate) line (anatomic anorectal line)
4–5 cm
Deep external sphincter
Internal sphincter
Anal valve
2½–3 cm
Anal crypt
Surgical anal canal
Anatomic anal canal
Superficial external sphincter
Perianal gland
½–1½ cm
Perianal space
Subcutaneous external sphincter
Hairs and sweat glands in perianal skin
Pecten
Anoderm
External hemorrhoidal plexus in perianal space
Intersphincteric line (white line of Hilton; intermuscular groove)

FIGURE 7.21 STRUCTURE OF THE RECTUM AND ANAL CANAL

The terminal end of the large intestine is the rectum and anal canal. Normally, the anal canal is closed due to the tonic contraction of the internal (smooth muscle) and external (skeletal muscle) anal sphincters. When the rectum is distended by fecal material, the internal sphincter relaxes but defecation does not occur until the voluntary external sphincter is relaxed and the muscles of the distal colon and rectum contract.

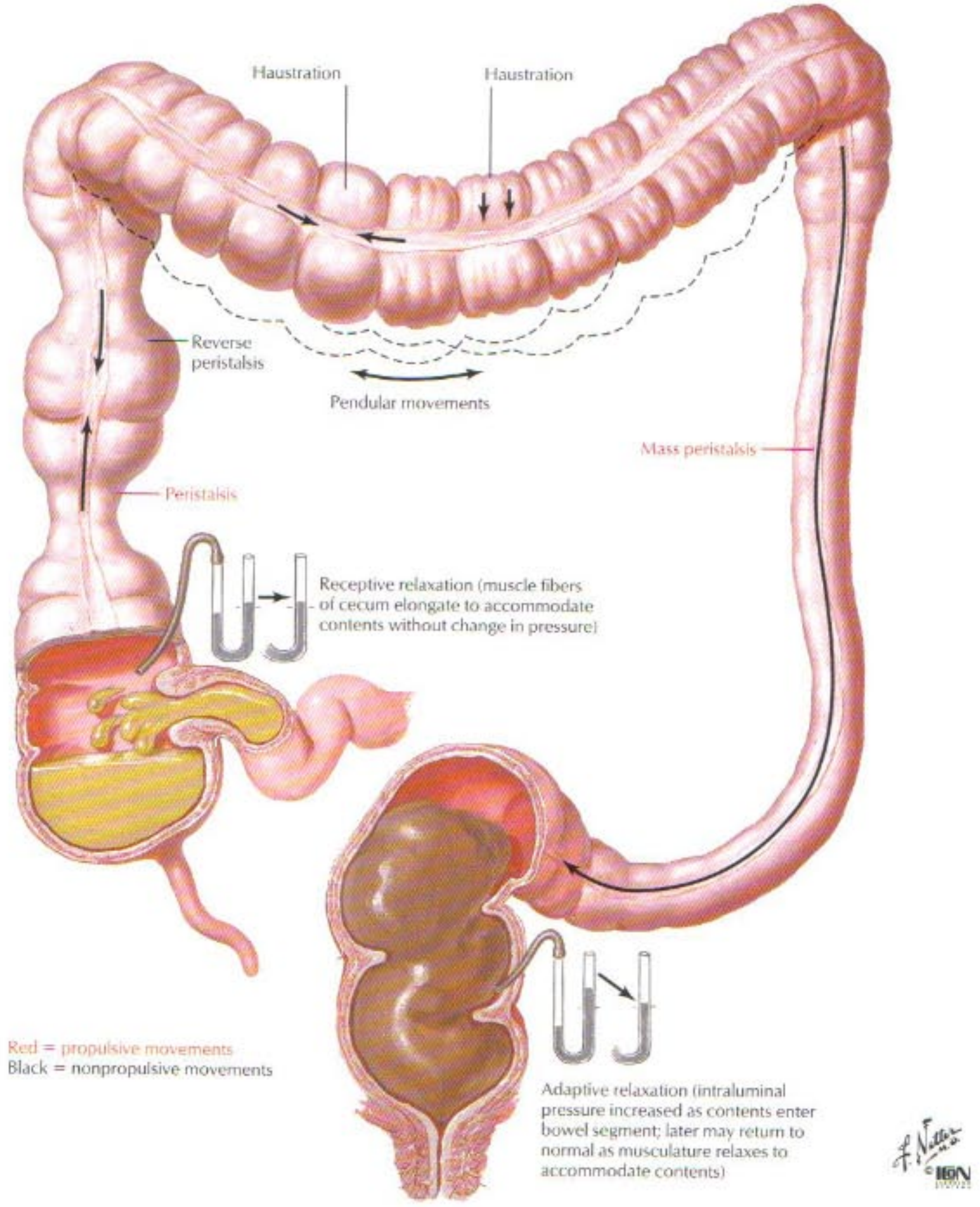
Haustration
Haustration
Reverse peristalsis
Pendular movements
Mass peristalsis
Peristalsis
Receptive relaxation (muscle fibers of cecum elongate to accommodate contents without change in pressure)
Red = propulsive movements
Black = nonpropulsive movements
Adaptive relaxation (intraluminal pressure increased as contents enter bowel segment; later may return to normal as musculature relaxes to accommodate contents)

FIGURE 7.22 COLONIC MOTILITY

Motility patterns in the colon include those that propel luminal contents toward the rectum (i.e., peristalsis and mass peristalsis) and those that prolong contact of the luminal contents with the absorptive epithelial cells. These later patterns allow sufficient contact time for maximal absorption of fluid from the feces. Conditions that promote the propulsive patterns result in diarrhea.

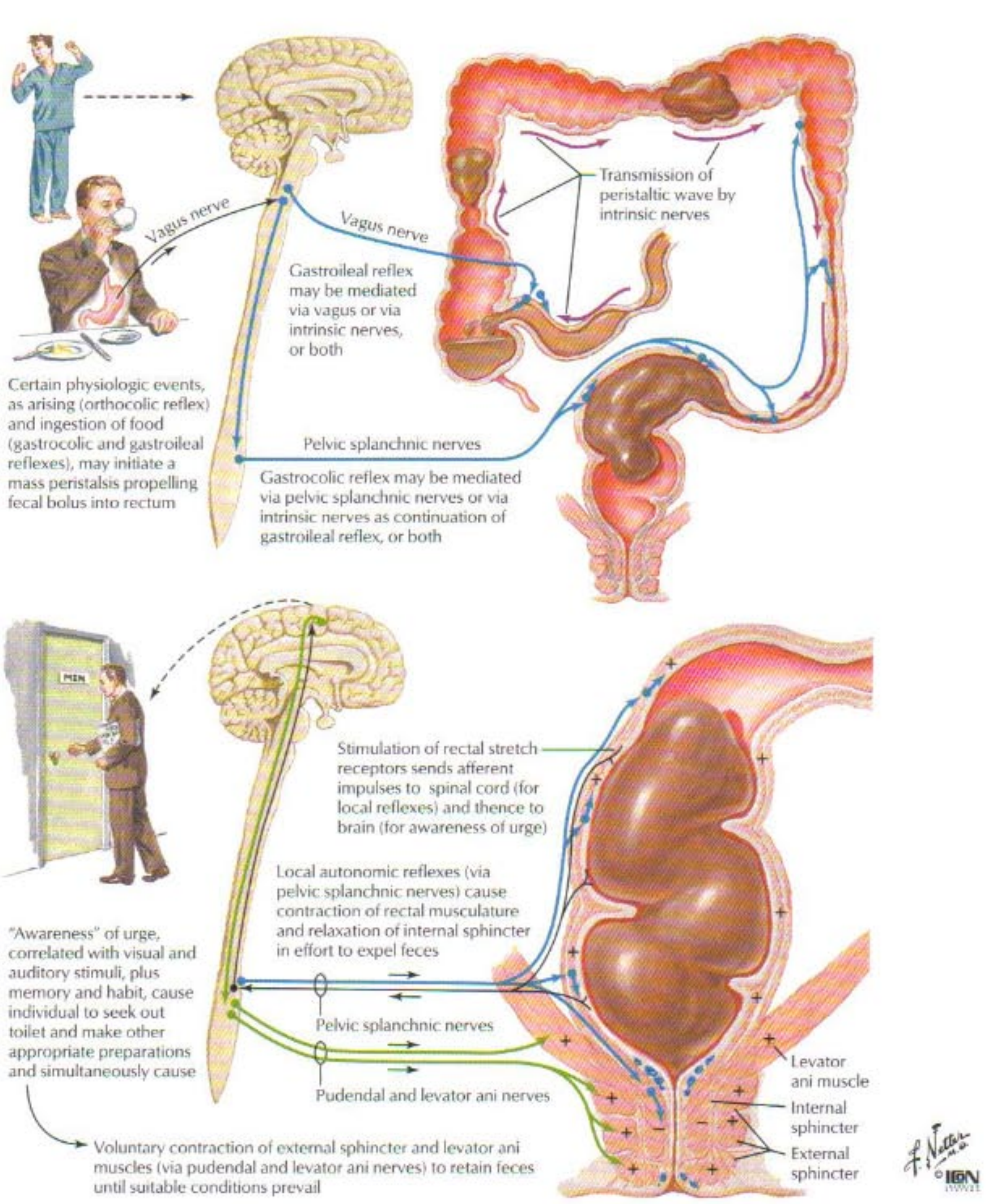
Vagus nerve
Vagus nerve
Transmission of peristaltic wave by intrinsic nerves
Gastroileal reflex may be mediated via vagus or via intrinsic nerves, or both
Certain physiologic events, as arising (orthocolic reflex) and ingestion of food (gastrocolic and gastroileal reflexes), may initiate a mass peristalsis propelling fecal bolus into rectum
Pelvic splanchnic nerves
Gastrocolic reflex may be mediated via pelvic splanchnic nerves or via intrinsic nerves as continuation of gastroileal reflex, or both
MEN
Stimulation of rectal stretch receptors sends afferent impulses to spinal cord (for local reflexes) and thence to brain (for awareness of urge)
Local autonomic reflexes (via pelvic splanchnic nerves) cause contraction of rectal musculature and relaxation of internal sphincter in effort to expel feces
"Awareness" of urge, correlated with visual and auditory stimuli, plus memory and habit, cause individual to seek out toilet and make other appropriate preparations and simultaneously cause
Pelvic splanchnic nerves
Pudendal and levator ani nerves
Voluntary contraction of external sphincter and levator ani muscles (via pudendal and levator ani nerves) to retain feces until suitable conditions prevail
Levator ani muscle
Internal sphincter
External sphincter
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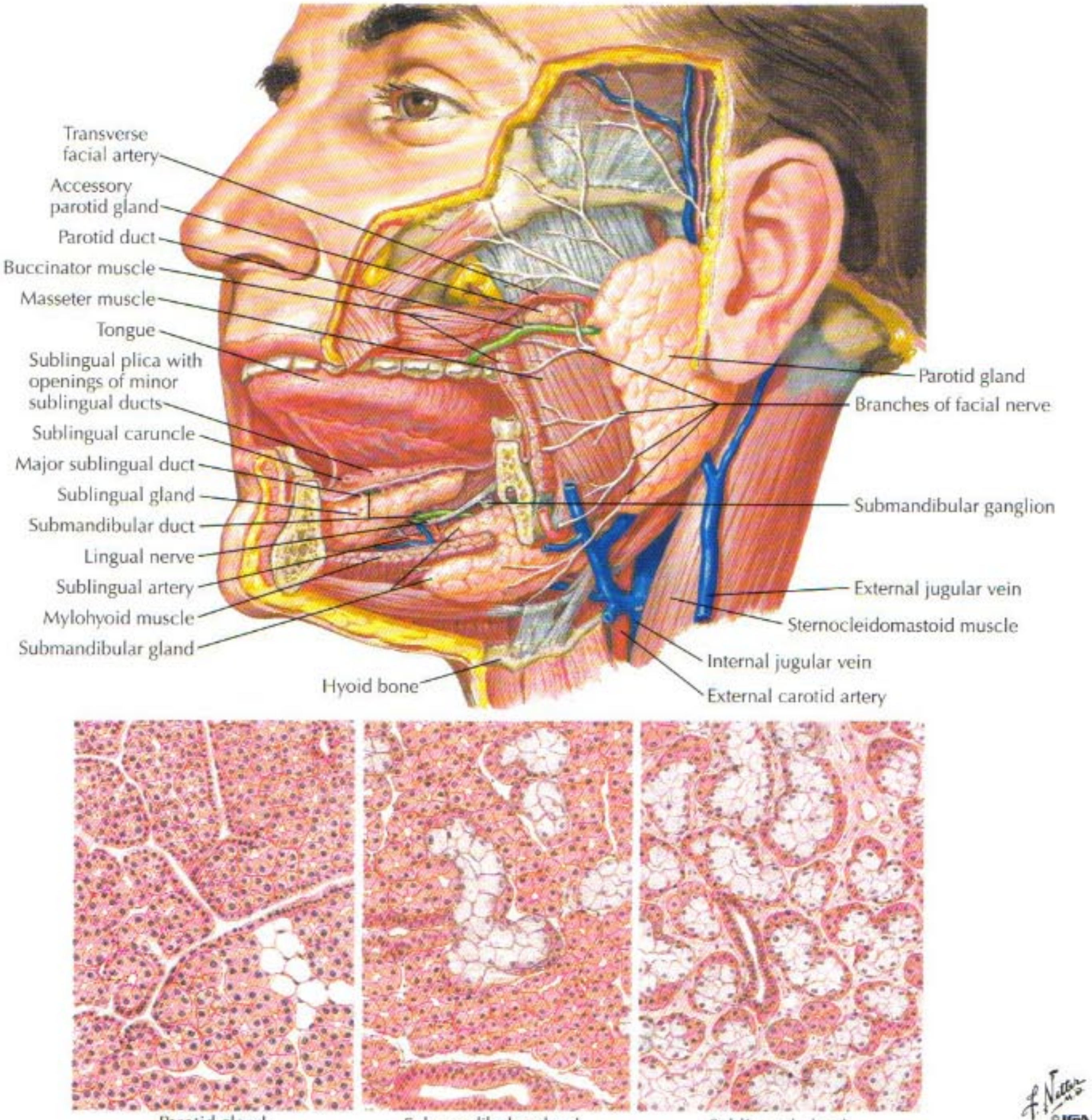
FIGURE 7.23 DEFECATION

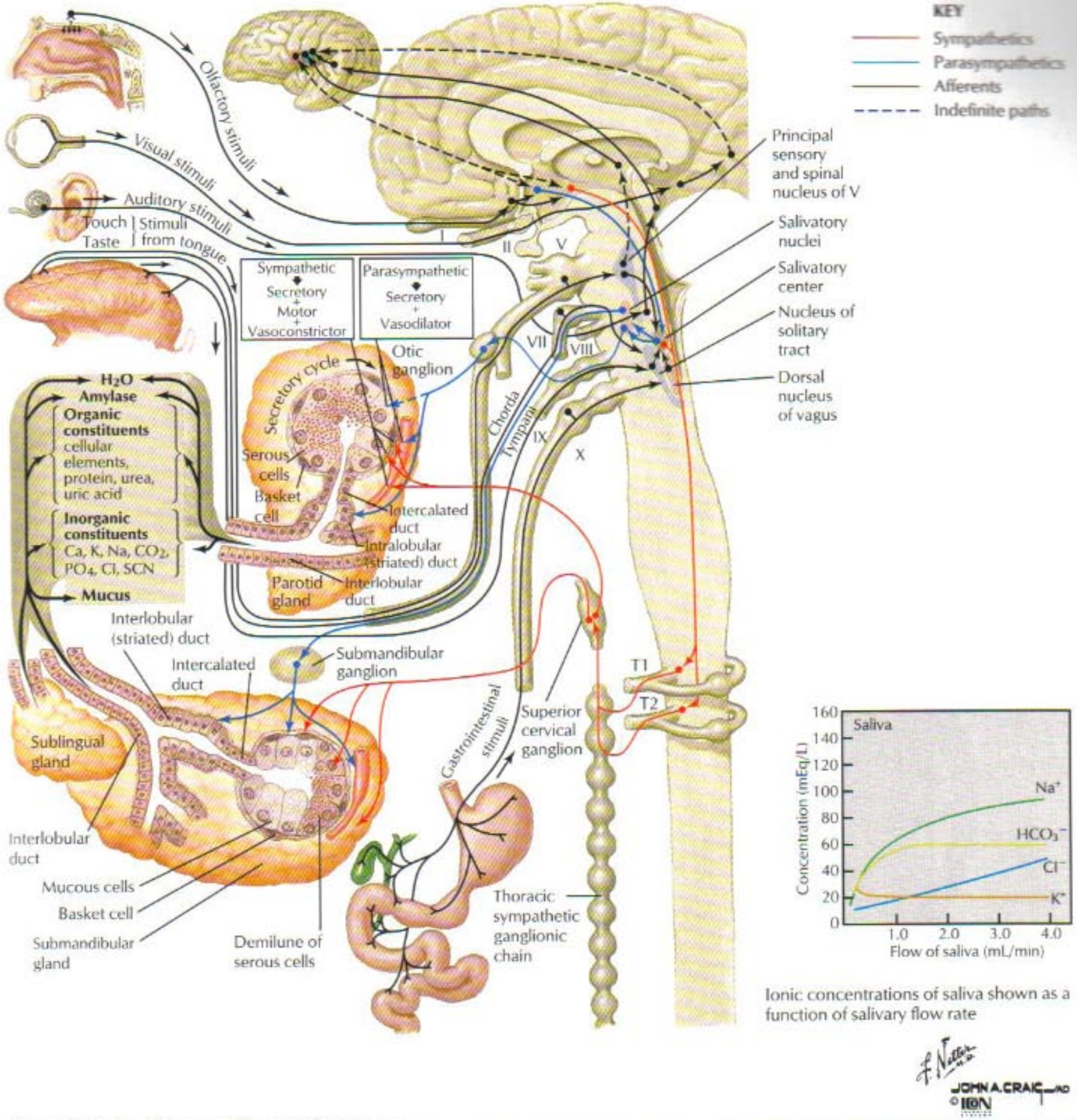
Defecation involves heeding the rectosphincteric reflex and relaxation of both the involuntary internal anal sphincter (innervated by the pelvic splanchnic nerves of the parasympathetic division of the autonomic nervous system) and voluntary external anal sphincter (innervated by the somatic pudendal nerve). Contraction of the distal colon and rectum expels the feces.


Transverse facial artery
Accessory parotid gland
Parotid duct
Buccinator muscle
Masseter muscle
Tongue
Sublingual plica with openings of minor sublingual ducts
Sublingual caruncle
Major sublingual duct
Sublingual gland
Submandibular duct
Lingual nerve
Sublingual artery
Mylohyoid muscle
Submandibular gland
Hyoid bone
Parotid gland
Branches of facial nerve
Submandibular ganglion
External jugular vein
Sternocleidomastoid muscle
Internal jugular vein
External carotid artery

Parotid gland Submandibular gland Sublingual gland

FIGURE 7.24 SALIVARY GLAND STRUCTURE

The salivary glands serve several functions, including keeping the oral cavity moist and lubricated to protect it from abrasion, controlling oral bacteria by secreting lysozyme, liquefying the food (thereby allowing molecules within the food to interact with and stimulate the taste buds), secreting calcium and phosphate for tooth formation and maintenance, and secreting amylase to begin digestion of starches. The serous acinar cells secrete the protein and enzymatic components of saliva, whereas the mucous acinar cells secrete a watery (low-mucin) mucus. The parotid gland is composed entirely of serous acini. The sublingual gland contains predominately mucous acini, with some serous acini as well. The submandibular gland contains a mixture of serous and mucous acini. Lingual lipase (secreated by von Ebner's serous glands of the tongue) mixes with the saliva and begins the digestion of fats.


KEY
Sympathetics
Parasympathetics
Afferents
Indefinite paths
Olfactory stimuli
Visual stimuli
Auditory stimuli
Touch | Stimuli
Taste | from tongue
Sympathetic
Secretory
+
Motor
+
Vasoconstrictor
Parasympathetic
Secretory
+
Vasodilator
Otic ganglion
Secretory cycle
H₂O
Amylase
Organic constituents
cellular elements, protein, urea, uric acid
Inorganic constituents
Ca, K, Na, CO₂, PO₄, Cl, SCN
Mucus
Serous cells
Basket cell
Intercalated duct
Intralobular (striated) duct
Parotid gland
Interlobular duct
Interlobular (striated) duct
Intercalated duct
Submandibular ganglion
Sublingual gland
Interlobular duct
Mucous cells
Basket cell
Submandibular gland
Demilune of serous cells
Gastrointestinal stimuli
Superior cervical ganglion
Thoracic sympathetic ganglionic chain
Chorda tympani
II
V
VII
VIII
IX
X
T1
T2
Principal sensory and spinal nucleus of V
Salivatory nuclei
Salivatory center
Nucleus of solitary tract
Dorsal nucleus of vagus
Saliva
Concentration (mEq/L)
160
140
120
100
80
60
40
20
0
Na⁺
HCO₃⁻
Cl⁻
K⁺
1.0
2.0
3.0
4.0
Flow of saliva (mL/min)
F. Netter M.D.
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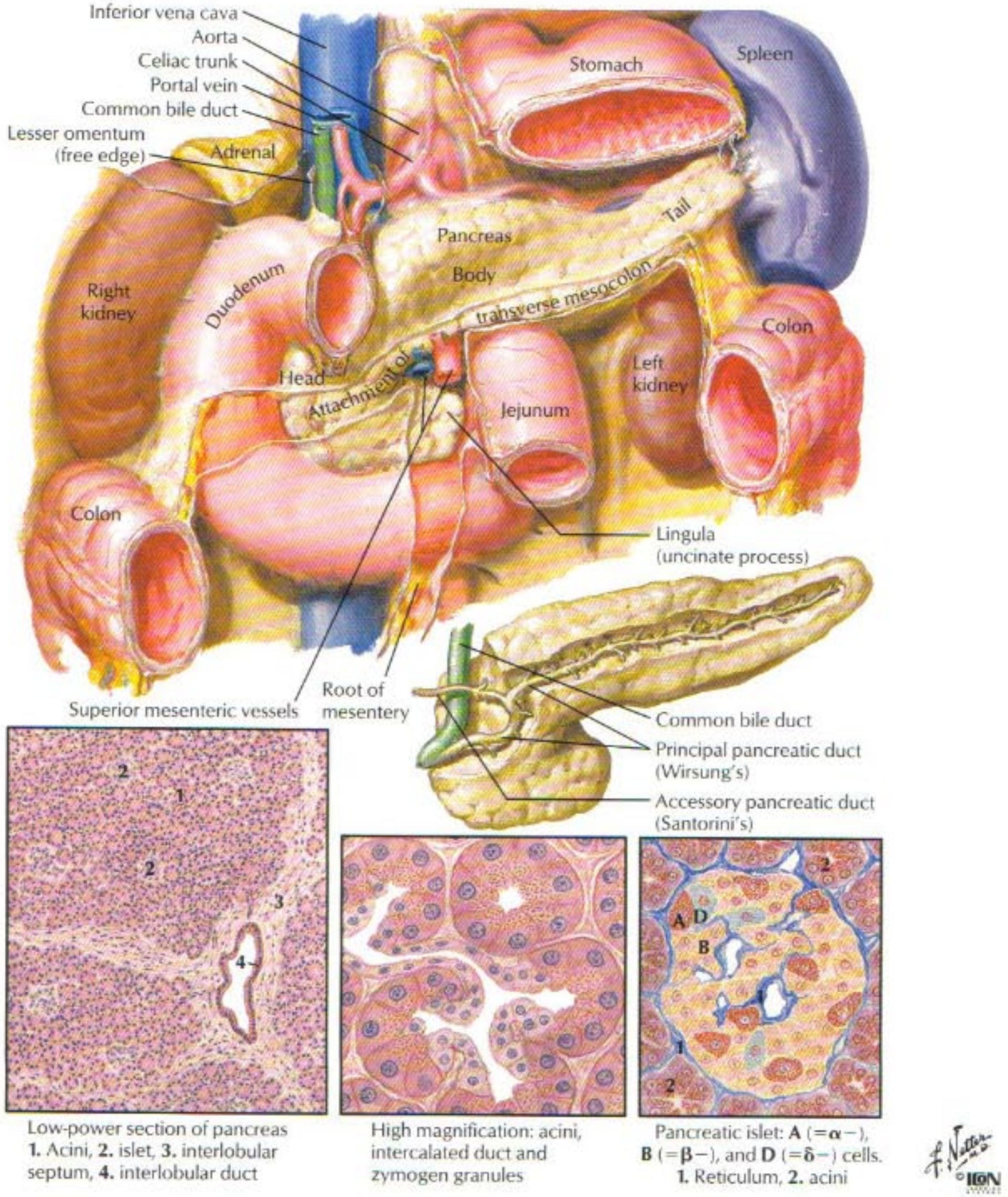
Ionic concentrations of saliva shown as a function of salivary flow rate

FIGURE 7.25 SALIVARY GLAND SECRETION

The salivary gland is under autonomic control. The glands receive both sympathetic and parasympathetic input. Of these, the parasympathetic system is more important in stimulating secretion. The acinar cells secrete the protein (serous cells) and mucus (mucous cells) components of saliva. The acini also secrete a fluid component that has a composition similar to that of plasma. As the saliva makes its way out of the gland, the ductal cells modify its electrolyte composition by active transport, such that the saliva entering the mouth is hypotonic to plasma and has a high bicarbonate concentration.


Inferior vena cava
Aorta
Celiac trunk
Portal vein
Common bile duct
Lesser omentum (free edge)
Adrenal
Stomach
Spleen
Pancreas
Tail
Body
transverse mesocolon
Attachment of
Right kidney
Duodenum
Head
Jejunum
Left kidney
Colon
Colon
Lingula (uncinate process)
Superior mesenteric vessels
Root of mesentery
Common bile duct
Principal pancreatic duct (Wirsung's)
Accessory pancreatic duct (Santorini's)
1
2
2
3
4
A
D
B
1
1
2
2
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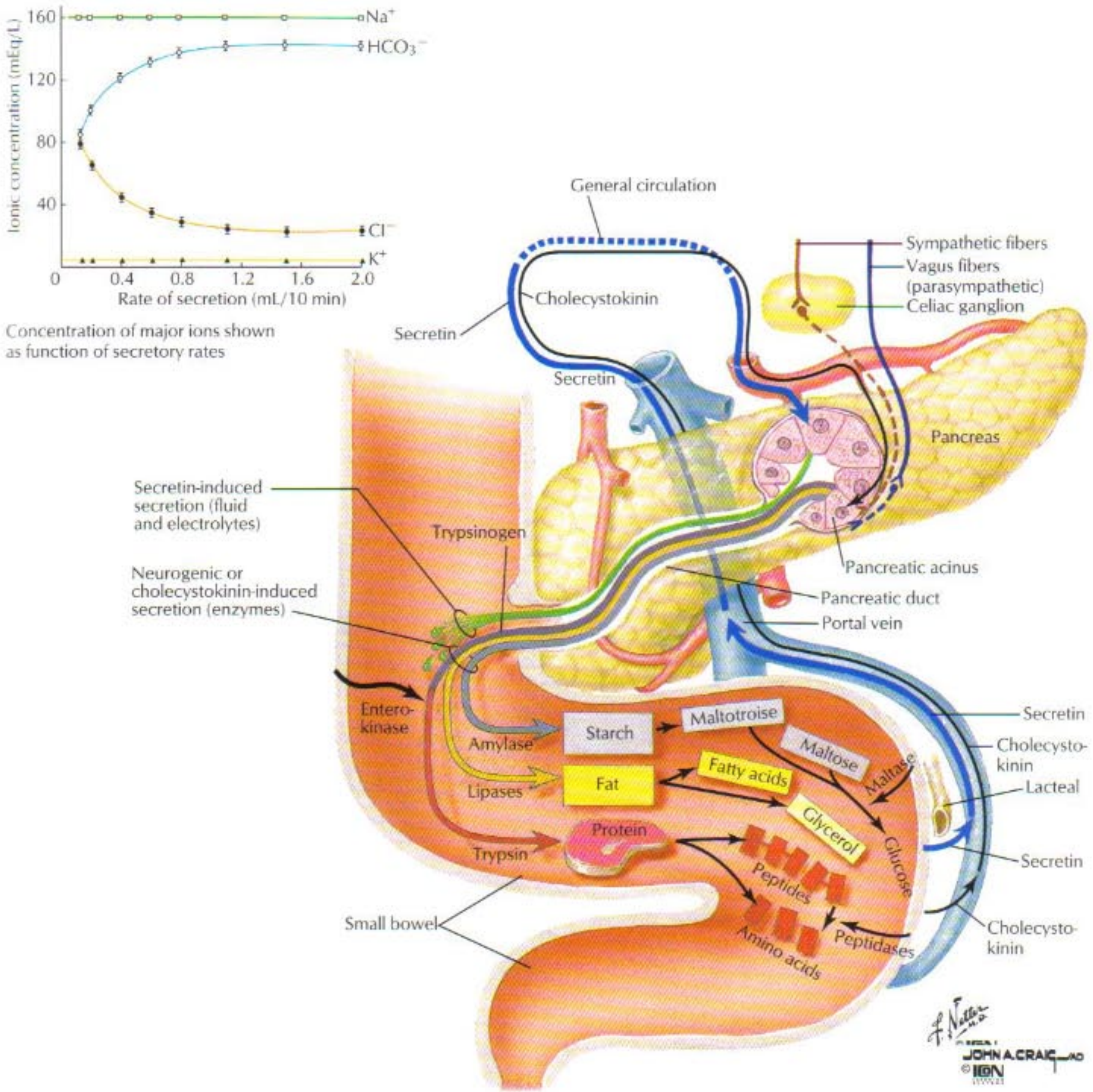
Low-power section of pancreas **1.** Acini, **2.** islet, **3.** interlobular septum, **4.** interlobular duct

High magnification: acini, intercalated duct and zymogen granules

Pancreatic islet: **A** $(=\alpha-)$, **B** $(=\beta-)$, and **D** $(=\delta-)$ cells. **1.** Reticulum, **2.** acini

FIGURE 7.26 PANCREAS STRUCTURE

The pancreas has exocrine and endocrine components. The acinar cells of the exocrine pancreas secrete a number of enzymes that are necessary for digestion of protein, starches, and fats. The ductal cells secrete fluid, with a high HCO_3^- content. This HCO_3^- serves to neutralize the acid entering the duodenum from the stomach. The endocrine pancreas consists of the islets of Langerhans. Within the islets, the A- or α-cells (located in the periphery of the islet) secrete glucagon, the B- or β-cells (located centrally in the islet) secrete insulin, and the D- or δ-cells (dispersed throughout the islet) secrete somatostatin.


Ionic concentration (mEq/L)
160
120
80
40
0
0.4
0.8
1.2
1.6
2.0
Rate of secretion (mL/10 min)
Na⁺
HCO₃⁻
Cl⁻
K⁺
General circulation
Sympathetic fibers
Vagus fibers (parasympathetic)
Celiac ganglion
Cholecystokinin
Secretin
Secretin
Pancreas
Secretin-induced secretion (fluid and electrolytes)
Trypsinogen
Neurogenic or cholecystokinin-induced secretion (enzymes)
Pancreatic acinus
Pancreatic duct
Portal vein
Entero-kinase
Amylase
Starch
Maltotroise
Maltose
Maltase
Lipases
Fat
Fatty acids
Glycerol
Glucose
Protein
Trypsin
Peptides
Amino acids
Peptidases
Secretin
Cholecysto-kinin
Lacteal
Secretin
Cholecysto-kinin
Small bowel
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Concentration of major ions shown as function of secretory rates

Figure 7.27 Pancreas Secretion

Secretion by the pancreas in under neural and hormonal control. The parasympathetic system (vagus nerve) stimulates secretion. Secretin is secreted by the neuroendocrine S cells in response to the presence of acid in the duodenum. It acts on the ductal cells of the pancreas to stimulate the secretion of fluid with a high HCO_3^- content. Cholecystokinin is secreted by I cells in response to fats in the duodenum and upper jejunum. It acts on the acinar cells to stimulate the secretion of enzymes. *Not shown in the figure:* Trypsin in the lumen of the duodenum activates other protease precursors (chymotrypsinogen and procarboxypeptidase) to their active forms (chymotrypsin and carboxypeptidase). *Note:* Secretin and CCK are secreted throughout the duodenum, especially proximally.

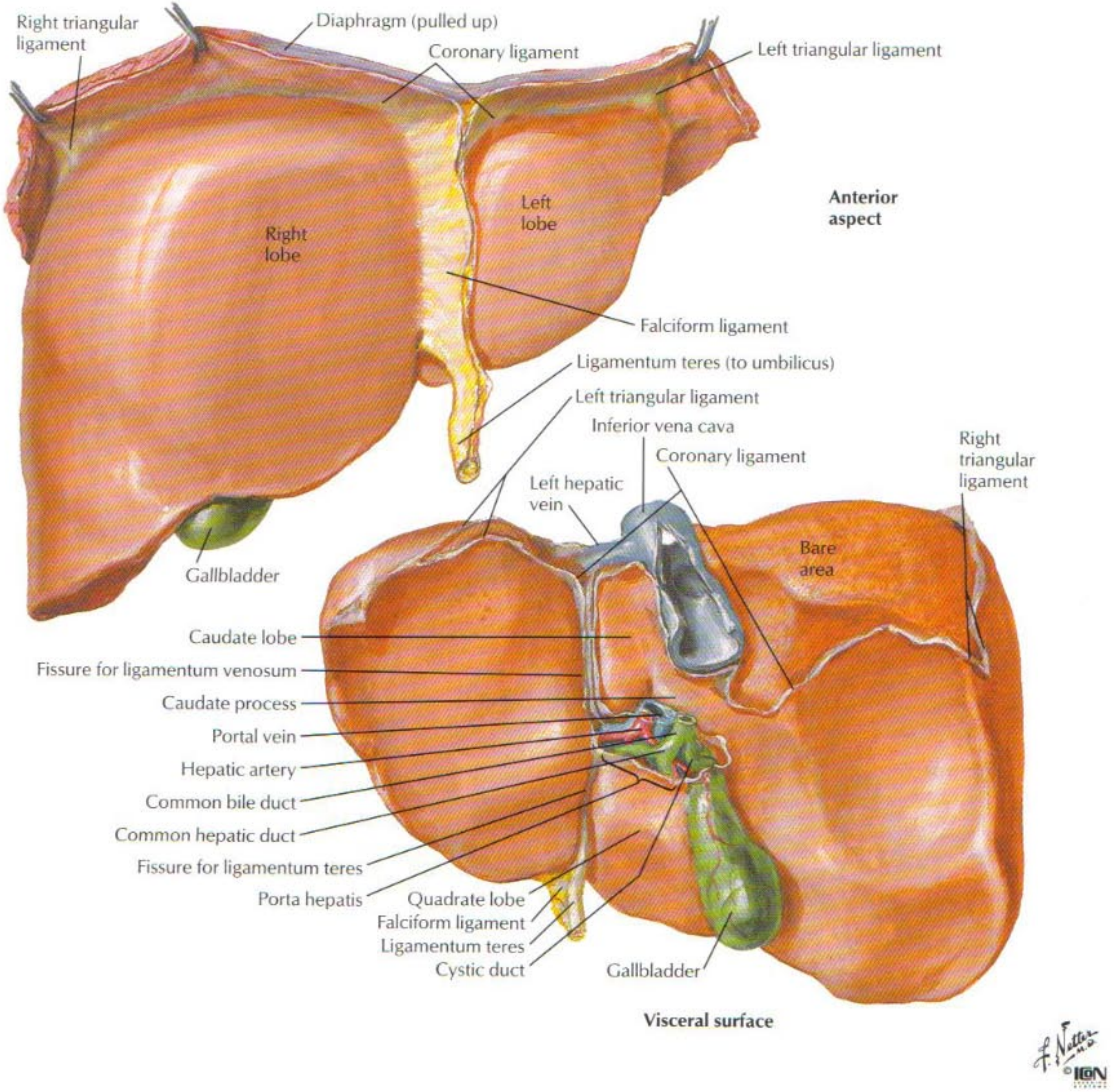
Right triangular ligament
Diaphragm (pulled up)
Coronary ligament
Left triangular ligament
Anterior aspect
Left lobe
Right lobe
Falciform ligament
Ligamentum teres (to umbilicus)
Left triangular ligament
Inferior vena cava
Coronary ligament
Right triangular ligament
Left hepatic vein
Gallbladder
Bare area
Caudate lobe
Fissure for ligamentum venosum
Caudate process
Portal vein
Hepatic artery
Common bile duct
Common hepatic duct
Fissure for ligamentum teres
Porta hepatis
Quadrate lobe
Falciform ligament
Ligamentum teres
Cystic duct
Gallbladder
Visceral surface
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FIGURE 7.28 LIVER STRUCTURE

The liver is the largest gland in the body and consists of four anatomical lobes (right, left, quadrate, and caudate). Various ligaments attach the liver to the overlying diaphragm (coronary ligaments) and anterior abdominal wall (falciform ligament). Functionally, the liver has two lobes (right and left), and each lobe receives arterial blood from the hepatic artery and portal venous blood from the abdominal GI tract. Each lobe also possesses its own venous and biliary drainage.

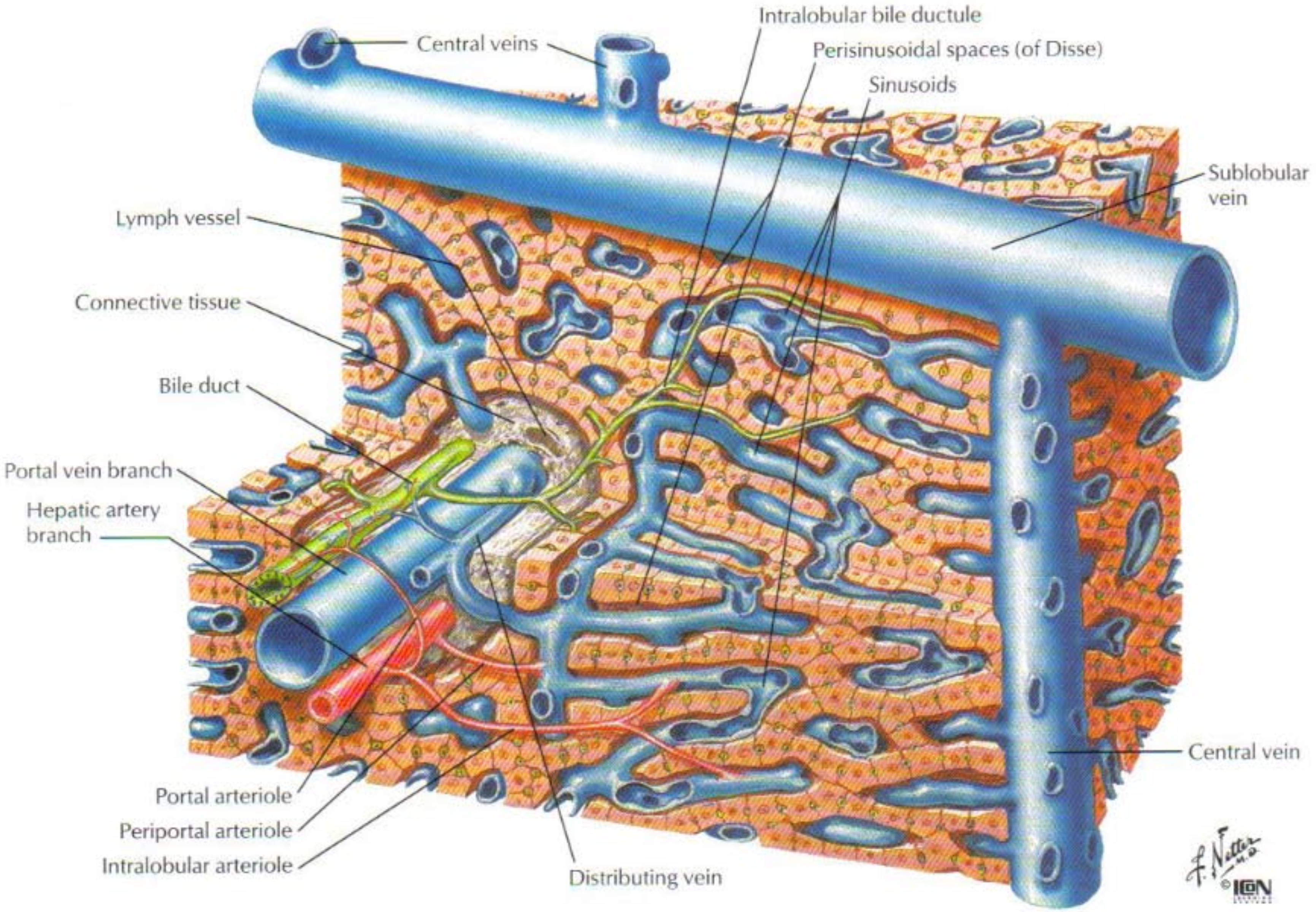
Central veins
Intralobular bile ductule
Perisinusoidal spaces (of Disse)
Sinusoids
Sublobular vein
Lymph vessel
Connective tissue
Bile duct
Portal vein branch
Hepatic artery branch
Central vein
Portal arteriole
Periportal arteriole
Intralobular arteriole
Distributing vein
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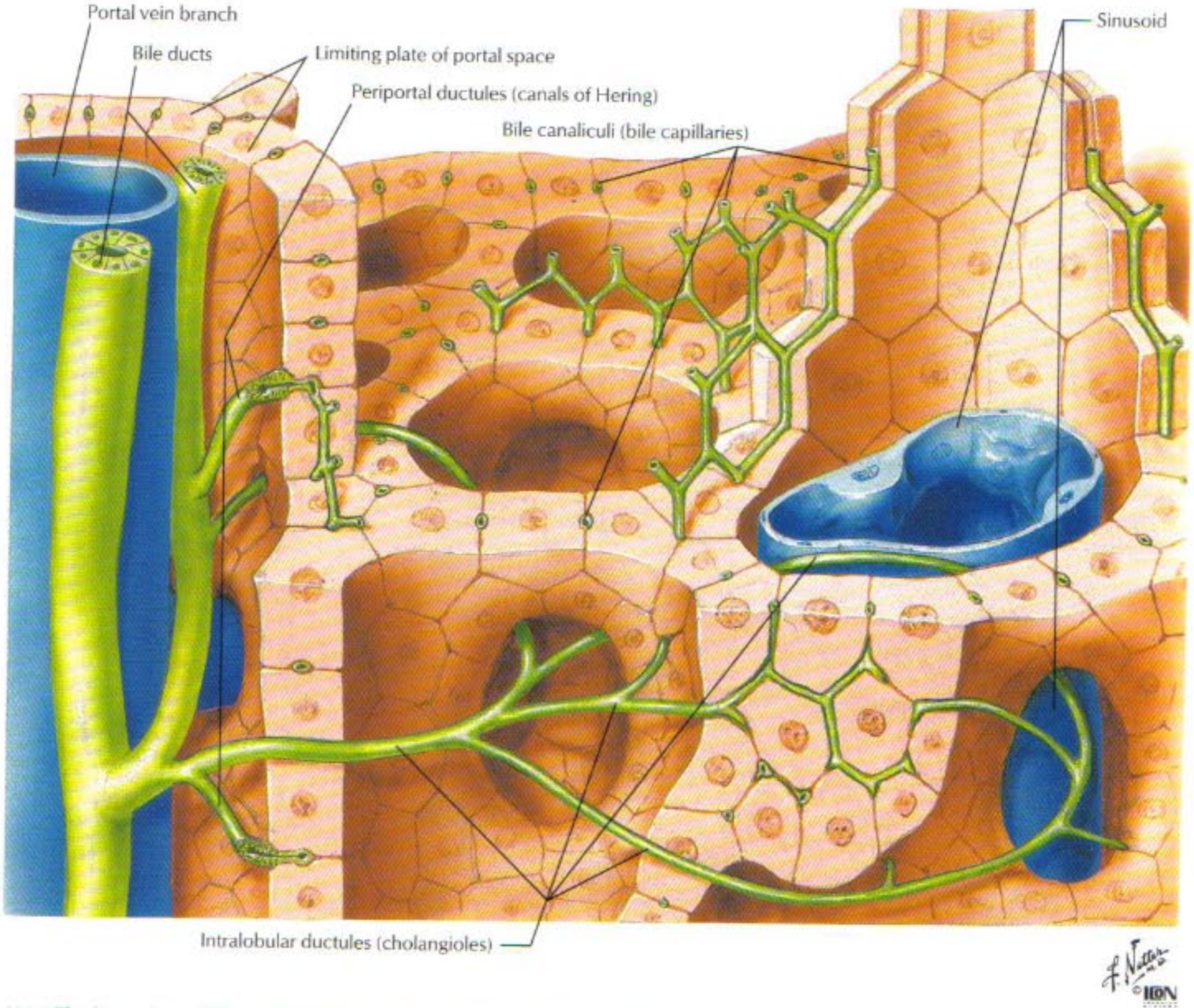
Figure 7.29 Liver Ultrastructure

The liver cells (hepatocytes) receive blood from the portal circulation (75%) and from the hepatic artery (25%). Hepatocytes are arranged in plates of cells that are separated from each other by hepatic sinusoids. The blood moves from the portal vein and hepatic arteriole branches through the sinusoids to the central vein. From the central vein, blood flows into the hepatic veins and inferior vena cava. The sinusoids are lined by a discontinuous endothelium that allows free movement of proteins from the blood to the hepatocytes, as well as from the hepatocytes to the blood. The sinusoids also contain phagocytic cells (Kupffer cells) that clear damaged red blood cells and foreign antigens (not shown). Bile is produced by the hepatocytes and drains into intralobular bile ductules and then larger bile ducts (right and left). The bile ducts coarse with the hepatic artery and portal vein. Ultimately, bile is collected into the gallbladder, where it is stored and concentrated.


Portal vein branch
Bile ducts
Limiting plate of portal space
Periportal ductules (canals of Hering)
Bile canaliculi (bile capillaries)
Sinusoid
Intralobular ductules (cholangioles)
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Note: The figure shows bile canaliculi as structures with walls of their own. However, boundaries of canaliculi are really a specialization of surface membranes of adjacent liver cells

FIGURE 7.30 INTRAHEPATIC BILIARY SYSTEM

The hepatocytes secrete bile into the bile canaliculi (approximately 900 mL/day of bile is produced). Bile flows from the canaliculi to the intralobular ductules and then empties into the bile ducts that run with the portal vein and hepatic artery branches. In between meals, approximately half of the hepatic bile is stored and concentrated in the gallbladder. Consequently, bile that reaches the duodenum is a mixture of the more dilute bile directly from the liver and concentrated bile from the gallbladder.

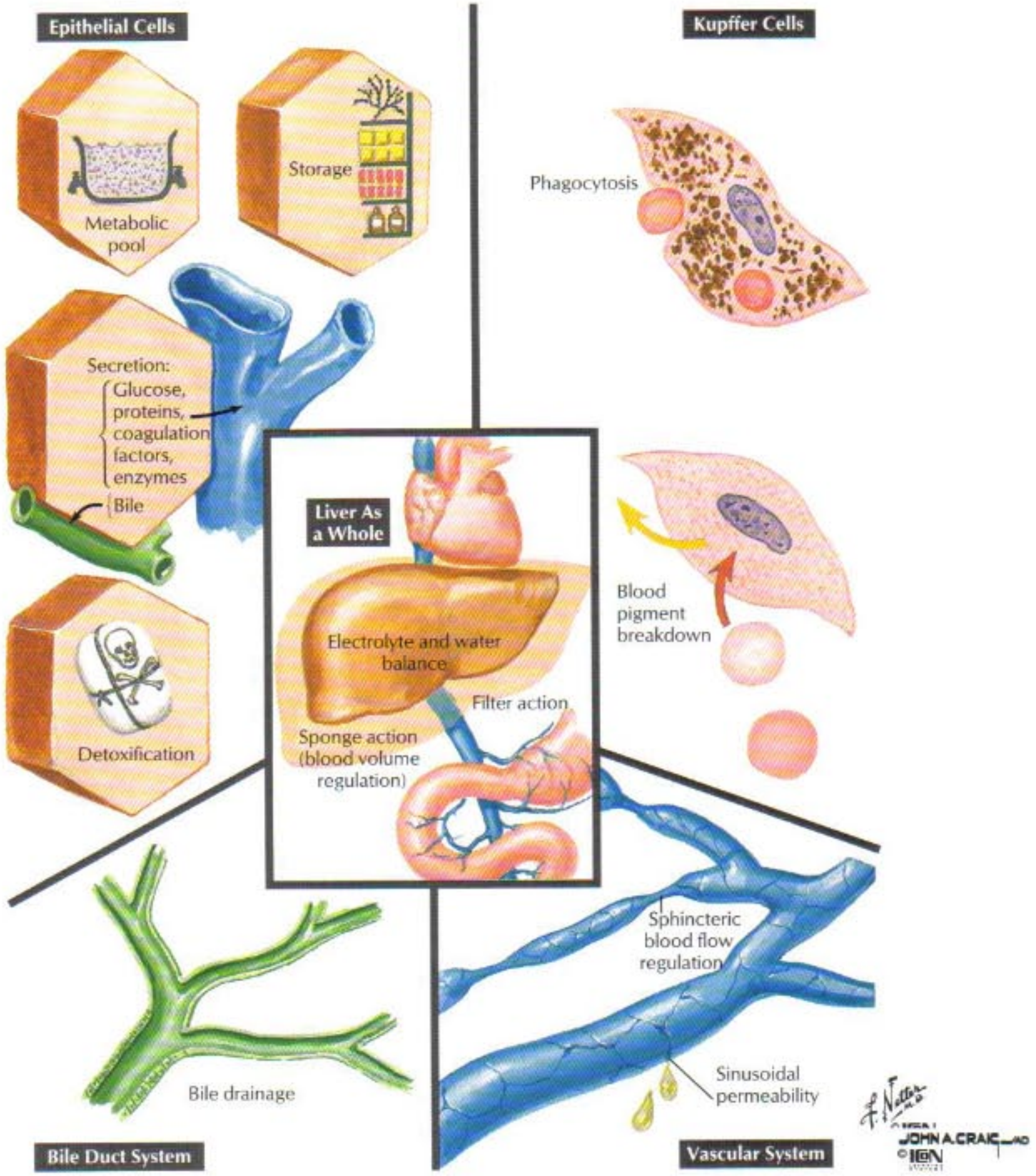
Epithelial Cells
Metabolic pool
Storage
Secretion:
Glucose,
proteins,
coagulation
factors,
enzymes
Bile
Detoxification
Kupffer Cells
Phagocytosis
Liver As a Whole
Electrolyte and water balance
Filter action
Sponge action (blood volume regulation)
Blood pigment breakdown
Sphincteric blood flow regulation
Sinusoidal permeability
Bile drainage
Bile Duct System
Vascular System
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FIGURE 7.31 OVERVIEW OF LIVER FUNCTION

The liver serves a number of important functions, including storage of important products and energy sources (e.g., glycogen, fat, protein, and vitamins), production of cellular fuels (e.g., glucose, fatty acids, and keto acids), production of plasma proteins and clotting factors, metabolism of toxins and drugs, the excretion of substances (e.g., bilirubin), and the production of bile acids. The Kupffer cells phagocytose foreign materials that cross the wall of the GI tract and enter the portal circulation. Cells of the mononuclear phagocytic system (MPS), both in the liver (i.e., Kupffer cells) and throughout the body phagocytose damaged red blood cells. Bilirubin is a product of hemoglobin degradation, and it excreted by the liver in the bile (see Figure 7.32).

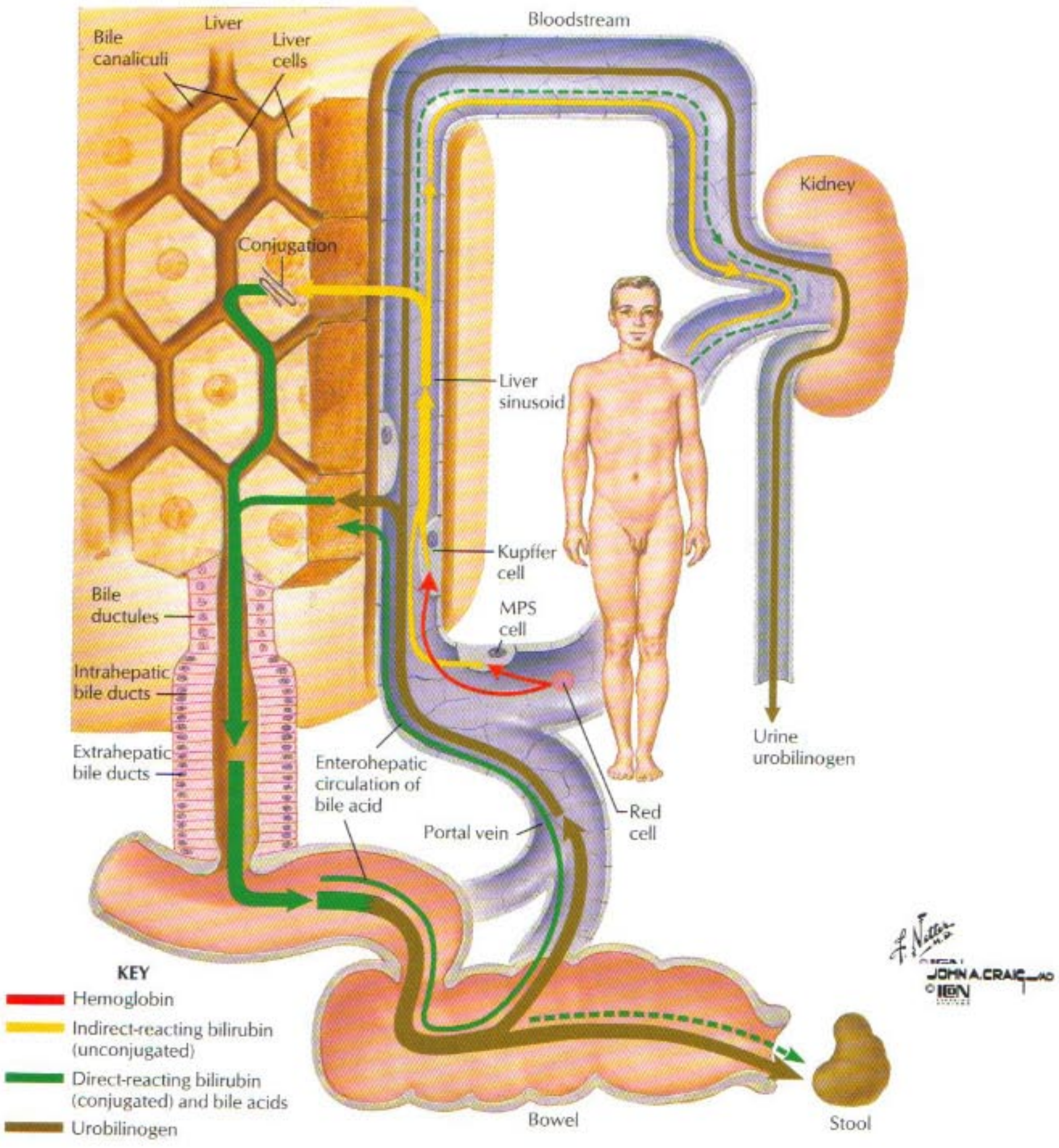
Bloodstream
Liver
Bile canaliculi
Liver cells
Kidney
Conjugation
Liver sinusoid
Kupffer cell
MPS cell
Bile ductules
Intrahepatic bile ducts
Extrahepatic bile ducts
Enterohepatic circulation of bile acid
Portal vein
Red cell
Urine urobilinogen
KEY
🟥 Hemoglobin
🟨 Indirect-reacting bilirubin (unconjugated)
🟩 Direct-reacting bilirubin (conjugated) and bile acids
🟫 Urobilinogen
Bowel
Stool
F. Netter M.D.
JOHN A. CRAIG AD
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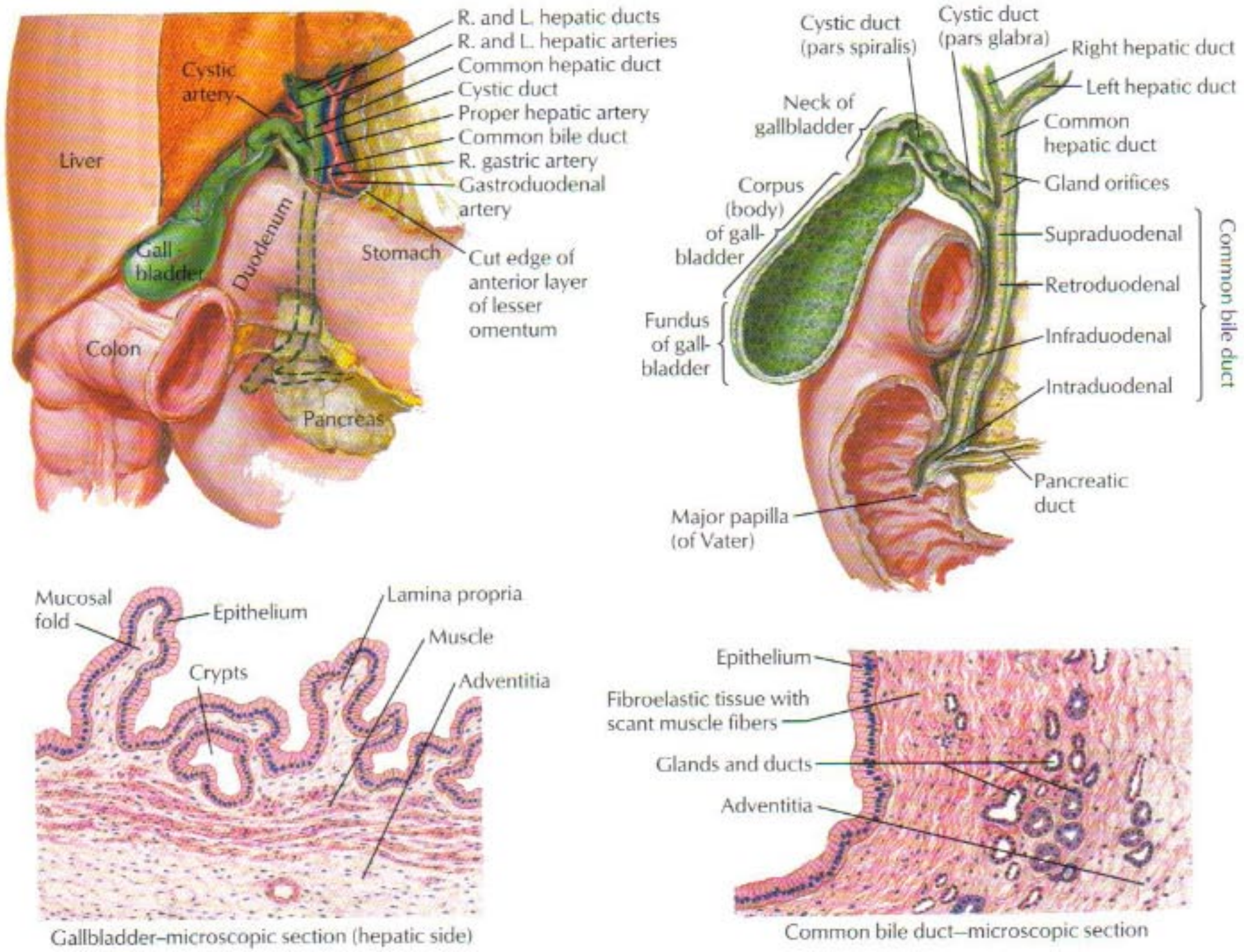
FIGURE 7.32 BILIRUBIN PRODUCTION AND EXCRETION

Cells of the mononuclear phagocytic system (MPS), both in the liver (i.e., Kupffer cells) and throughout the body, phagocytose damaged red blood cells. Bilirubin, a degradation product of hemoglobin, is produced by these cells (unconjugated bilirubin). The liver hepatocytes take up this bilirubin, conjugate it with glucuronic acid (conjugated bilirubin), and excrete it into the bile. In the intestine the bilirubin is converted to urobilinogen by bacterial action. Some of this urobilinogen is absorbed and returned to the liver, which reexcretes it in the bile. Some of the urobilinogen is also excreted by the kidneys. The bile also contains bile acids, which aid in the digestion of lipids by their ability to emulsify fats and form mixed micelles with the lipid molecules (see Figure 7.37). Bile acids are reabsorbed by the terminal ileum. Typically, 65% to 85% of the bile acids are recirculated in this manner (enterohepatic circulation). The bile acids lost in the feces each day are replaced by hepatic synthesis.


R. and L. hepatic ducts
R. and L. hepatic arteries
Common hepatic duct
Cystic duct
Proper hepatic artery
Common bile duct
R. gastric artery
Gastroduodenal artery
Cut edge of anterior layer of lesser omentum
Cystic artery
Liver
Gall bladder
Duodenum
Stomach
Colon
Pancreas
Cystic duct (pars spiralis)
Cystic duct (pars glabra)
Right hepatic duct
Left hepatic duct
Common hepatic duct
Gland orifices
Neck of gallbladder
Corpus (body) of gall-bladder
Fundus of gall-bladder
Supraduodenal
Retroduodenal
Infraduodenal
Intraduodenal
Common bile duct
Pancreatic duct
Major papilla (of Vater)
Mucosal fold
Epithelium
Crypts
Lamina propria
Muscle
Adventitia
Epithelium
Fibroelastic tissue with scant muscle fibers
Glands and ducts
Adventitia

Gallbladder–microscopic section (hepatic side)

Common bile duct–microscopic section

FIGURE 7.33 GALLBLADDER STRUCTURE AND FUNCTION

The gallbladder is a small hollow organ attached to the surface of the liver. It serves to store and concentrate the bile synthesized by the liver (holds about 20 to 50 mL of bile). Vagal stimulation and cholecystokinin released from neuroendocrine cells in the duodenum (in response to the presence of fat) cause the gallbladder to contract and transport bile down the cystic duct and the common bile duct, where it empties into the second (descending) portion of the duodenum. The gallbladder mucosa is specialized for electrolyte and water absorption, which allows the gallbladder to concentrate the bile.

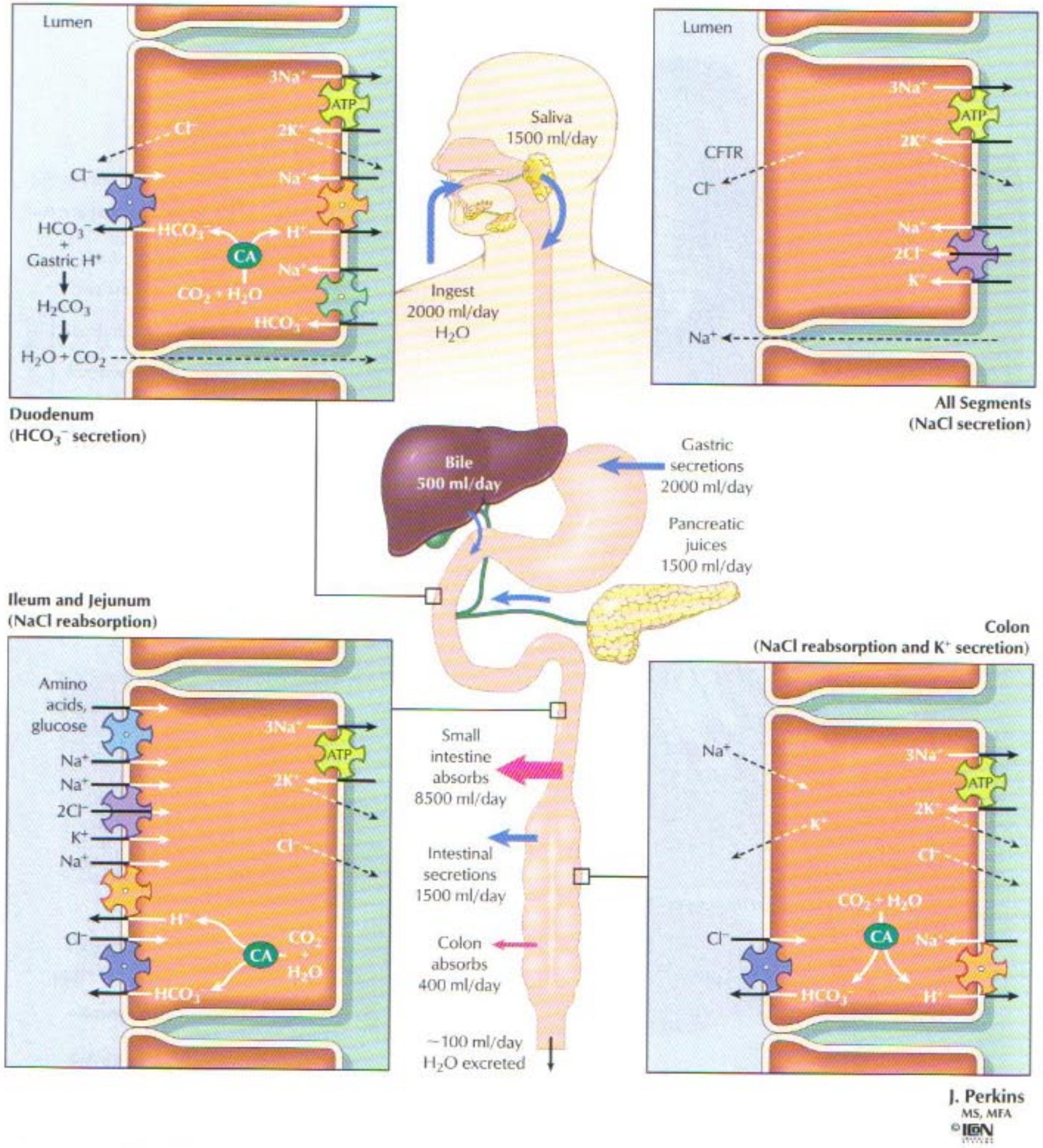

Lumen
3Na⁺
ATP
2K⁺
Cl⁻
Cl⁻
Na⁺
HCO_3^-
+
Gastric H⁺
H_2CO_3
$H_2O + CO_2$
HCO_3^-
H⁺
CA
Na⁺
$CO_2 + H_2O$
HCO_3^-
Duodenum
(HCO_3^- secretion)
Saliva
1500 ml/day
Ingest
2000 ml/day
H_2O
Lumen
3Na⁺
ATP
2K⁺
CFTR
Cl⁻
Na⁺
2Cl⁻
K⁺
Na⁺
All Segments
(NaCl secretion)
Bile
500 ml/day
Gastric
secretions
2000 ml/day
Pancreatic
juices
1500 ml/day
Ileum and Jejunum
(NaCl reabsorption)
Amino
acids,
glucose
Na⁺
Na⁺
2Cl⁻
K⁺
Na⁺
3Na⁺
ATP
2K⁺
Cl⁻
H⁺
Cl⁻
CA
CO_2
+
H_2O
HCO_3^-
Small
intestine
absorbs
8500 ml/day
Intestinal
secretions
1500 ml/day
Colon
absorbs
400 ml/day
~100 ml/day
H_2O excreted
Colon
(NaCl reabsorption and K⁺ secretion)
Na⁺
3Na⁺
ATP
2K⁺
K⁺
Cl⁻
$CO_2 + H_2O$
CA
Cl⁻
Na⁺
HCO_3^-
H⁺
J. Perkins
MS, MFA
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FIGURE 7.34 GI TRACT FLUID AND ELECTROLYTE TRANSPORT

Large volumes of fluid are secreted and absorbed by the GI tract each day. The secreted fluid helps maintain the intestinal contents in a liquefied state to aid digestion. Normally, this secreted fluid, along with any fluid ingested, is absorbed so that only 100 mL/day of water is excreted in the feces (with diarrhea, intestinal fluid loss can reach 20 L/day). Both the secretion of fluid and its absorption are driven by electrolyte transport. Secretion of NaCl drives fluid secretion, whereas the absorption of Na⁺ with Cl⁻ and other solutes drives absorption. The principal cellular mechanisms of intestinal electrolyte transport are illustrated. For simplicity, not all known mechanisms are shown. Also, cells may express multiple transport systems, which here are depicted as being present in different cells.

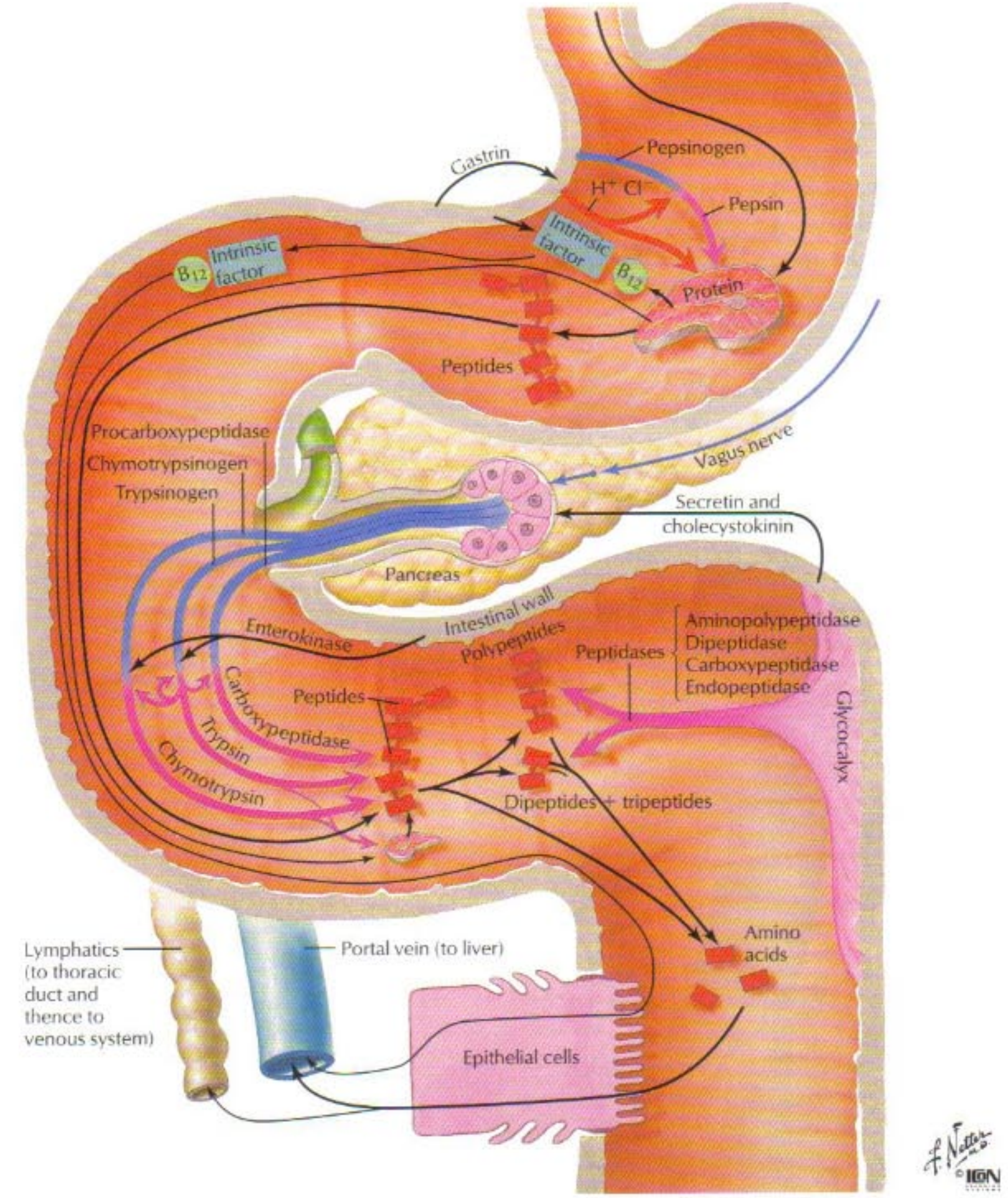
Gastrin
Pepsinogen
H⁺ Cl⁻
Pepsin
Intrinsic factor
B12
Intrinsic factor
B12
Protein
Peptides
Procarboxypeptidase
Chymotrypsinogen
Trypsinogen
Vagus nerve
Secretin and cholecystokinin
Pancreas
Intestinal wall
Polypeptides
Enterokinase
Peptidases
Aminopolypeptidase
Dipeptidase
Carboxypeptidase
Endopeptidase
Glycocalyx
Peptides
Carboxypeptidase
Trypsin
Chymotrypsin
Dipeptides + tripeptides
Amino acids
Lymphatics (to thoracic duct and thence to venous system)
Portal vein (to liver)
Epithelial cells

FIGURE 7.35 DIGESTION OF PROTEIN

Protein digestion begins in the stomach through the action of HCl and pepsin. Pancreatic proteases and peptidases associated with the glycocalyx of the intestinal epithelial cells continue this process, yielding amino acids, tripeptides, and dipeptides, which are then absorbed by the intestinal epithelial cells. The pancreas also secretes proelastase (not shown in figure). The tripeptides and dipeptides are absorbed coupled to H^+, while the amino acids are absorbed coupled to Na^+ (see Figure 7.34).

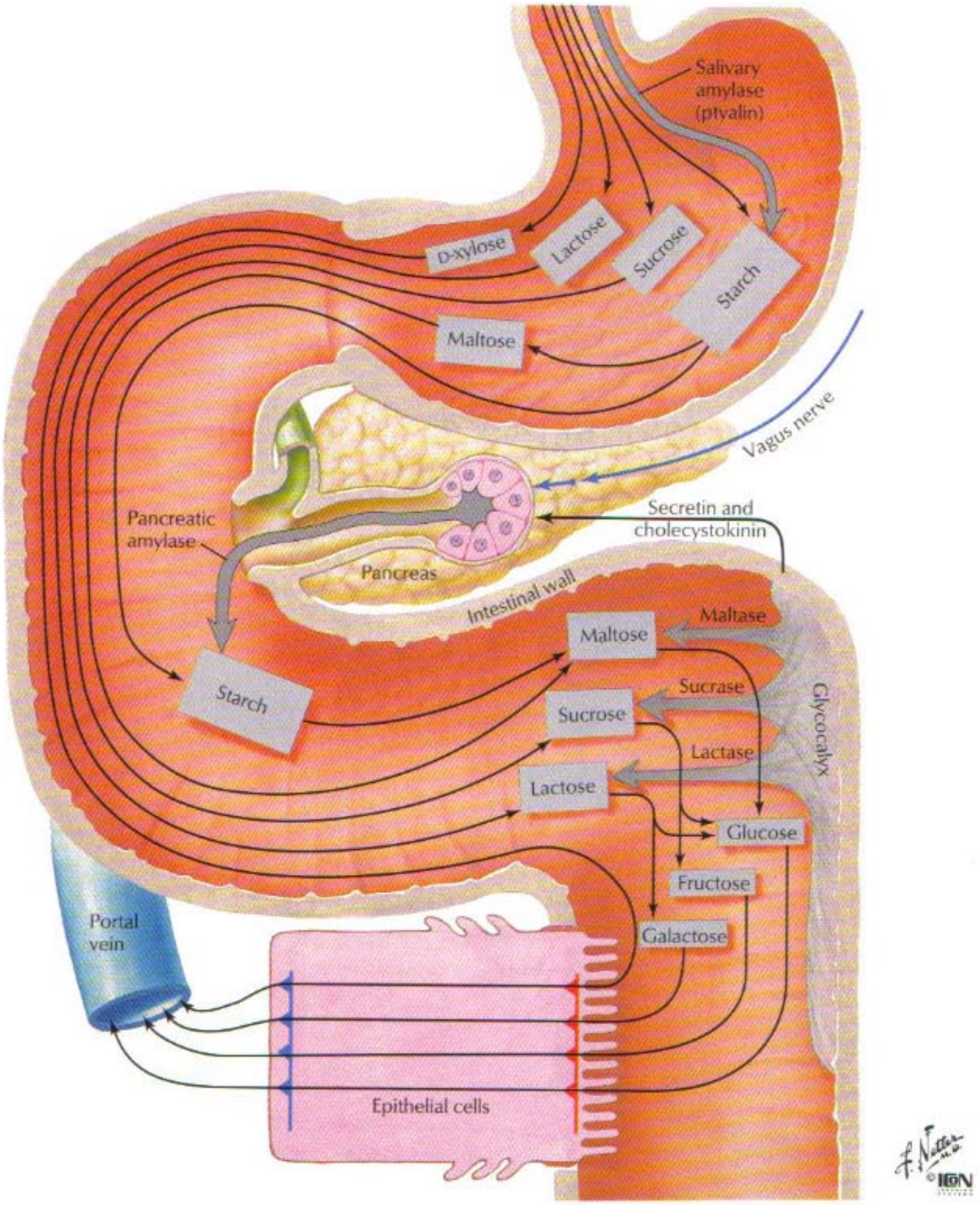
Salivary amylase (ptyalin)
D-xylose
Lactose
Sucrose
Starch
Maltose
Vagus nerve
Pancreatic amylase
Secretin and cholecystokinin
Pancreas
Intestinal wall
Maltase
Maltose
Starch
Sucrase
Sucrose
Lactase
Glycocalyx
Lactose
Glucose
Fructose
Galactose
Portal vein
Epithelial cells
F. Netter M.D.
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FIGURE 7.36 DIGESTION OF CARBOHYDRATES

Digestion of carbohydrates and starches begins in the mouth and stomach through the action of salivary amylase. Pancreatic amylase and enzymes associated with the glycocalyx of the intestinal epithelial cells continue this process, yielding monosaccharides. The glycocalyx also secretes isomaltase (not shown in figure). These monosaccharides are absorbed by the intestinal epithelial cells coupled to Na⁺ (see Figure 7.34).

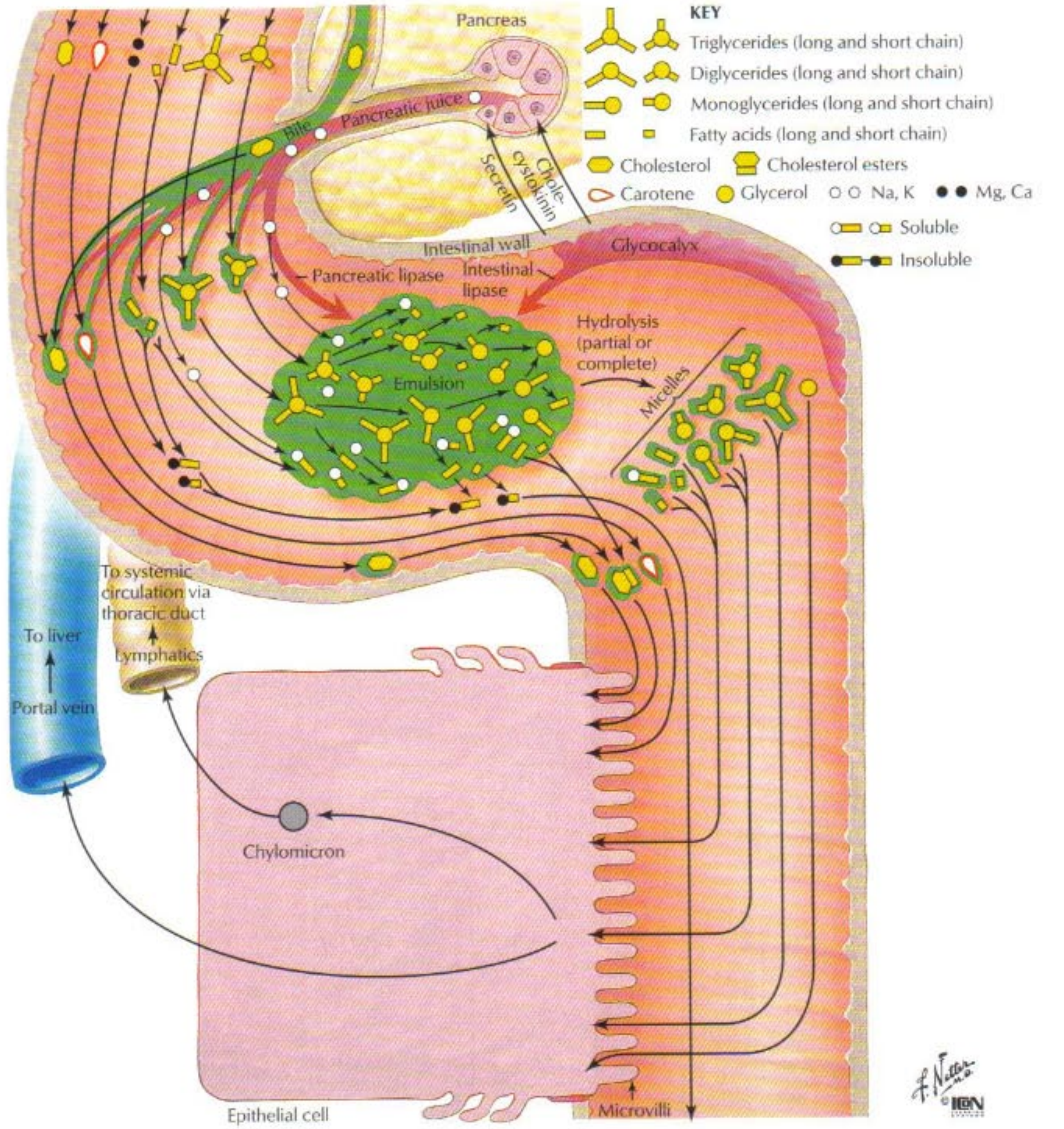
KEY
Triglycerides (long and short chain)
Diglycerides (long and short chain)
Monoglycerides (long and short chain)
Fatty acids (long and short chain)
Cholesterol
Cholesterol esters
Carotene
Glycerol
Na, K
Mg, Ca
Soluble
Insoluble
Pancreas
Pancreatic juice
Bile
Secretin
Cholecystokinin
Intestinal wall
Glycocalyx
Pancreatic lipase
Intestinal lipase
Hydrolysis (partial or complete)
Micelles
Emulsion
To systemic circulation via thoracic duct
Lymphatics
To liver
Portal vein
Chylomicron
Epithelial cell
Microvilli
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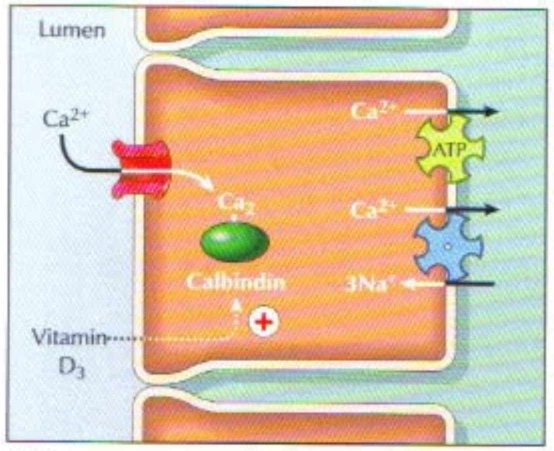
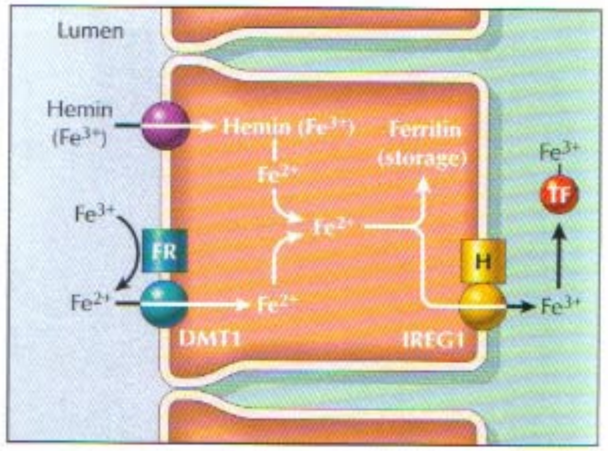
FIGURE 7.37 DIGESTION OF FAT

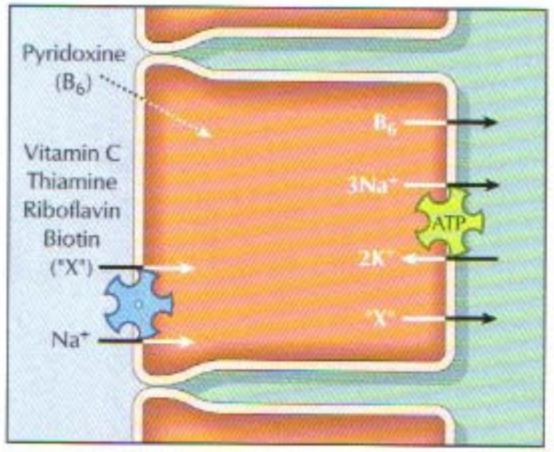
Although some fat digestion begins in the mouth and stomach, most occurs in the intestine, largely by the action of pancreatic lipases. Lipases associated with the glycocalyx of the epithelial cells also contribute to this process. The bile salts are critically important in this process because they emulsify the fats and form mixed micelles. Soluble glycerol and short- and medium-chain fatty acids are absorbed without micelle formation, pass through the epithelial cells, and are taken up in the portal circulation. The principal products of fat digestion are fatty acids (absorbed coupled to Na^+), monoglycerides, and cholesterol. Further processing within the epithelial cells results in chylomicron formation, and these chylomicrons are exocytosed at the basal membrane and taken up into lymphatic lacteals. They enter the thoracic duct and are eventually emptied into the venous system. Divalent cations in the lumen of the intestine can form insoluble complexes, preventing absorption. By this same mechanism, malabsorption of fat can impair intestinal Ca^{2+} absorption.


Lumen
Ca^{2+}
Ca^{2+}
ATP
Ca_2
Ca^{2+}
Calbindin
3Na^+
Vitamin D_3

Ca^{2+}

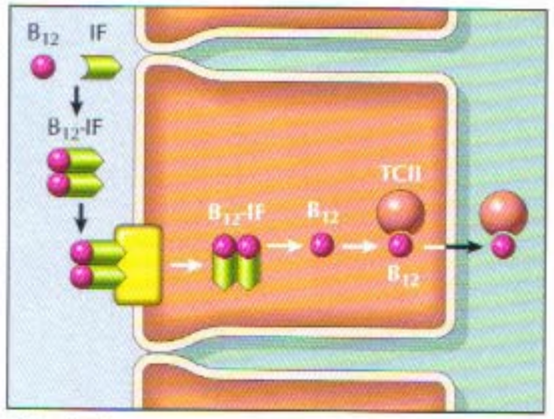

Lumen
Hemin (Fe^{3+})
Hemin (Fe^{3+})
Ferritin (storage)
Fe^{2+}
Fe^{3+}
TF
Fe^{3+}
FR
Fe^{2+}
H
Fe^{2+}
Fe^{2+}
Fe^{3+}
DMT1
IREG1

Iron

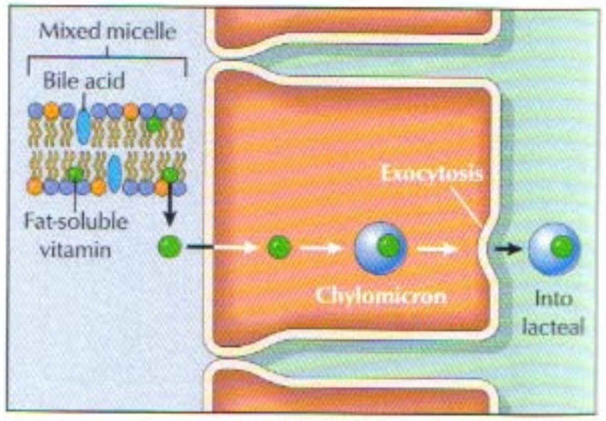

Pyridoxine (B_6)
B_6
Vitamin C
Thiamine
Riboflavin
Biotin
("X")
3Na^+
ATP
2K^+
"X"
Na^+

Water Soluble Vitamins

Element	Site of Absorption	Mechanism
Ca^{2+}	Duodenum and jejunum	Active
Fe^{2+}	Duodenum and jejunum	Facilitated diffusion
Water-Soluble Vitamins		
Vitamin C	Ileum	Na^+-coupled/2° active
Thiamin (B_1)	Jejunum	Na^+-coupled/2° active
Riboflavin (B_2)	Jejunum	Na^+-coupled/2° active
Biotin	Jejunum	Na^+-coupled/2° active
Vitamin B_{12}	Ileum	Facilitated diffusion
Pyridoxine (B_6)	Jejunum and ileum	Passive diffusion
Fat-Soluble Vitamins		
Vitamin A	Jejunum and ileum	Passive diffusion
Vitamin D	Jejunum and ileum	Passive diffusion
Vitamin E	Jejunum and ileum	Passive diffusion
Vitamin K	Jejunum and ileum	Passive diffusion


B_{12}
IF
B_{12}-IF
TCII
B_{12}-IF
B_{12}
B_{12}

Vitamin B_{12}


Mixed micelle
Bile acid
Exocytosis
Fat-soluble vitamin
Chylomicron
Into lacteal

Fat-Soluble Vitamins

J. Perkins
MS, MFA
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FIGURE 7.38 ABSORPTION OF ESSENTIAL VITAMINS AND ELEMENTS

The cell mechanisms involved in the absorption of Ca^{2+}, iron, and several important vitamins are summarized. Vitamin D_3 (1,25-dihydroxy-vitamin D_3) plays an important role in stimulating intestinal Ca^{2+} absorption. Intrinsic factor is made by the stomach (see Figure 7.12). If insufficient amounts of intrinsic factor are produced, B_{12} deficiency ensues. Failure to properly digest fats (see Figure 7.37) can lead to deficiencies of the fat-soluble vitamins. *Abbreviations: DMT1,* Divalent metal transporter 1; *FR,* ferrireductase; *H,* hephaestin; *IF,* intrinsic factor; *IREG1,* iron-regulated transporter 1; *TCII,* transcobalamin II; *TF,* transferrin.

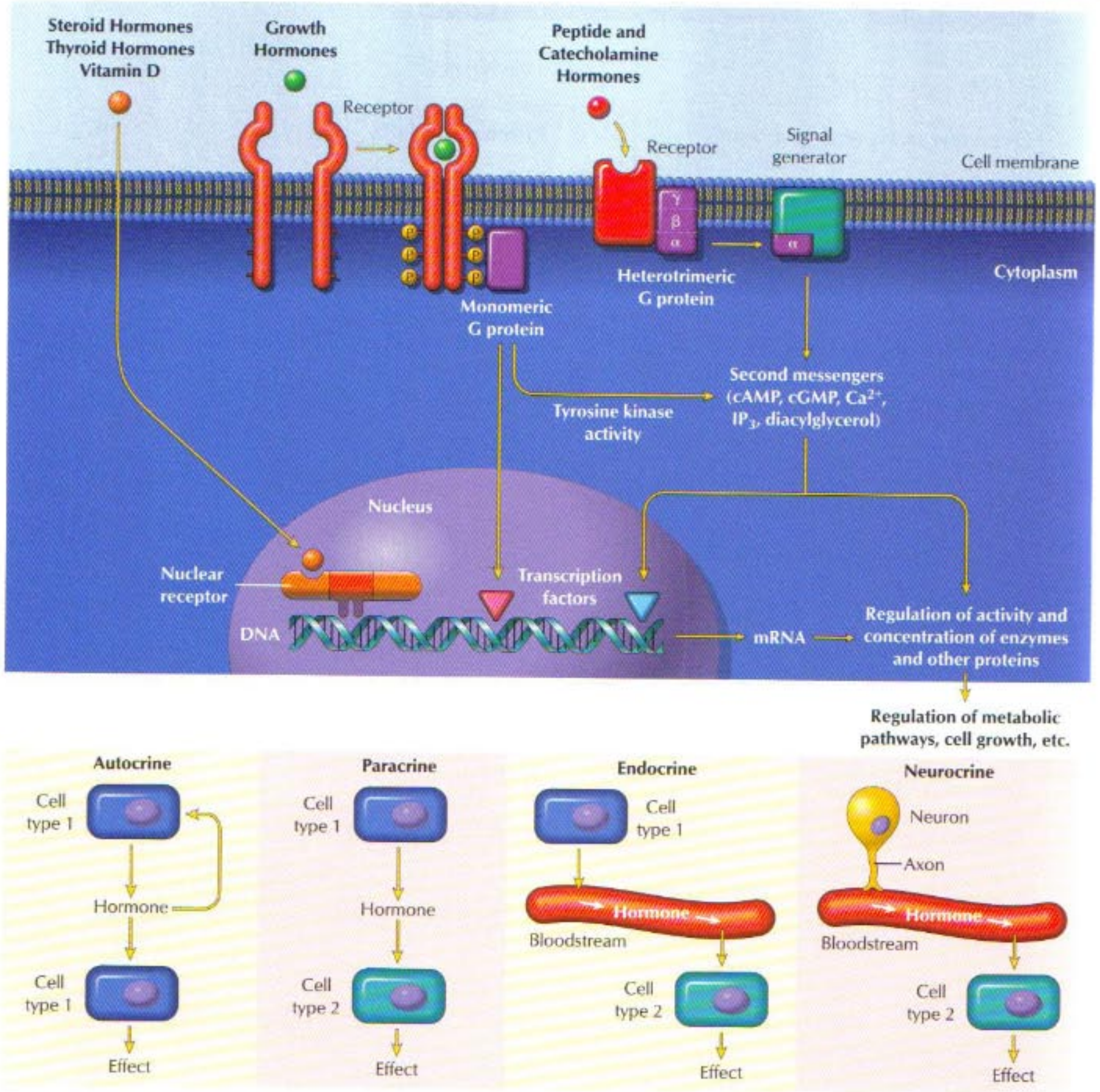
Steroid Hormones
Thyroid Hormones
Vitamin D
Growth Hormones
Receptor
Peptide and Catecholamine Hormones
Receptor
Signal generator
Cell membrane
γ
β
α
α
Heterotrimeric G protein
Cytoplasm
P
Monomeric G protein
Second messengers (cAMP, cGMP, Ca²⁺, IP₃, diacylglycerol)
Tyrosine kinase activity
Nucleus
Nuclear receptor
Transcription factors
DNA
mRNA
Regulation of activity and concentration of enzymes and other proteins
Regulation of metabolic pathways, cell growth, etc.
Autocrine
Cell type 1
Hormone
Cell type 1
Effect
Paracrine
Cell type 1
Hormone
Cell type 2
Effect
Endocrine
Cell type 1
Hormone
Bloodstream
Cell type 2
Effect
Neurocrine
Neuron
Axon
Hormone
Bloodstream
Cell type 2
Effect

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FIGURE 8.1 OVERVIEW OF HORMONE ACTION

Hormones are involved in the process of cell-to-cell signaling. Hormones interact with their target cells via specific hormone-receptor interactions (see Chart 1.2). The receptor may be in the plasma membrane or inside the cell (cytoplasmic or nuclear). The hormone-receptor interaction may generate second messengers or regulate gene expression. The effect of the hormone on the cell may be the result of altered metabolic pathways (i.e., changes in enzyme activity or concentrations of enzymes) or changes in cell structure and growth. The lower panel illustrates the different modes of cell-to-cell communication.

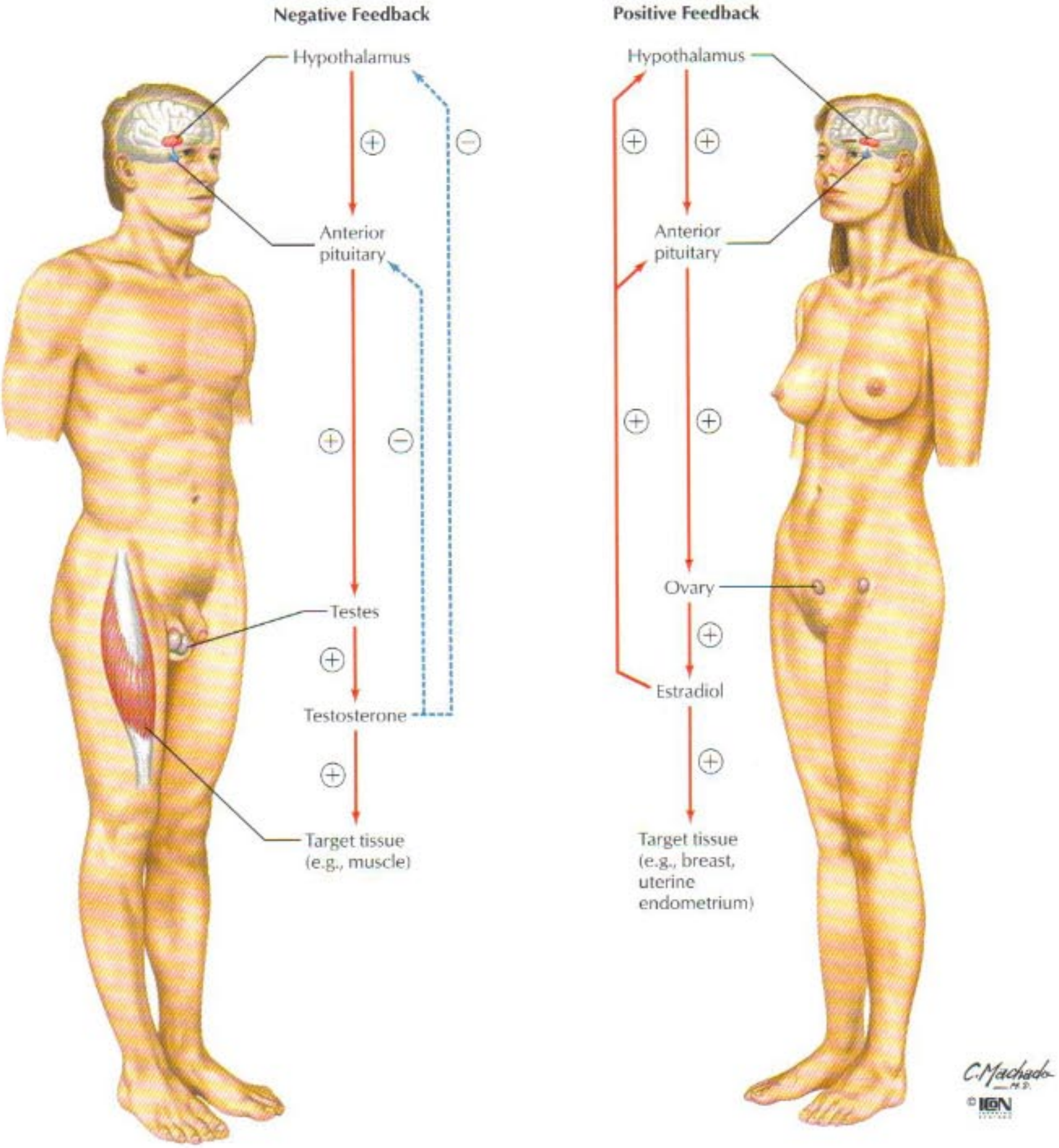
Negative Feedback
Hypothalamus
⊕
⊖
Anterior pituitary
⊕
⊖
Testes
⊕
Testosterone
⊕
Target tissue (e.g., muscle)
Positive Feedback
Hypothalamus
⊕
⊕
Anterior pituitary
⊕
⊕
Ovary
⊕
Estradiol
⊕
Target tissue (e.g., breast, uterine endometrium)
C. Machado M.D.
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FIGURE 8.2 FEEDBACK REGULATION

Hormone secretion is regulated by both negative feedback mechanisms (e.g., testosterone) and positive feedback mechanisms (e.g., follicular phase of the menstrual cycle).

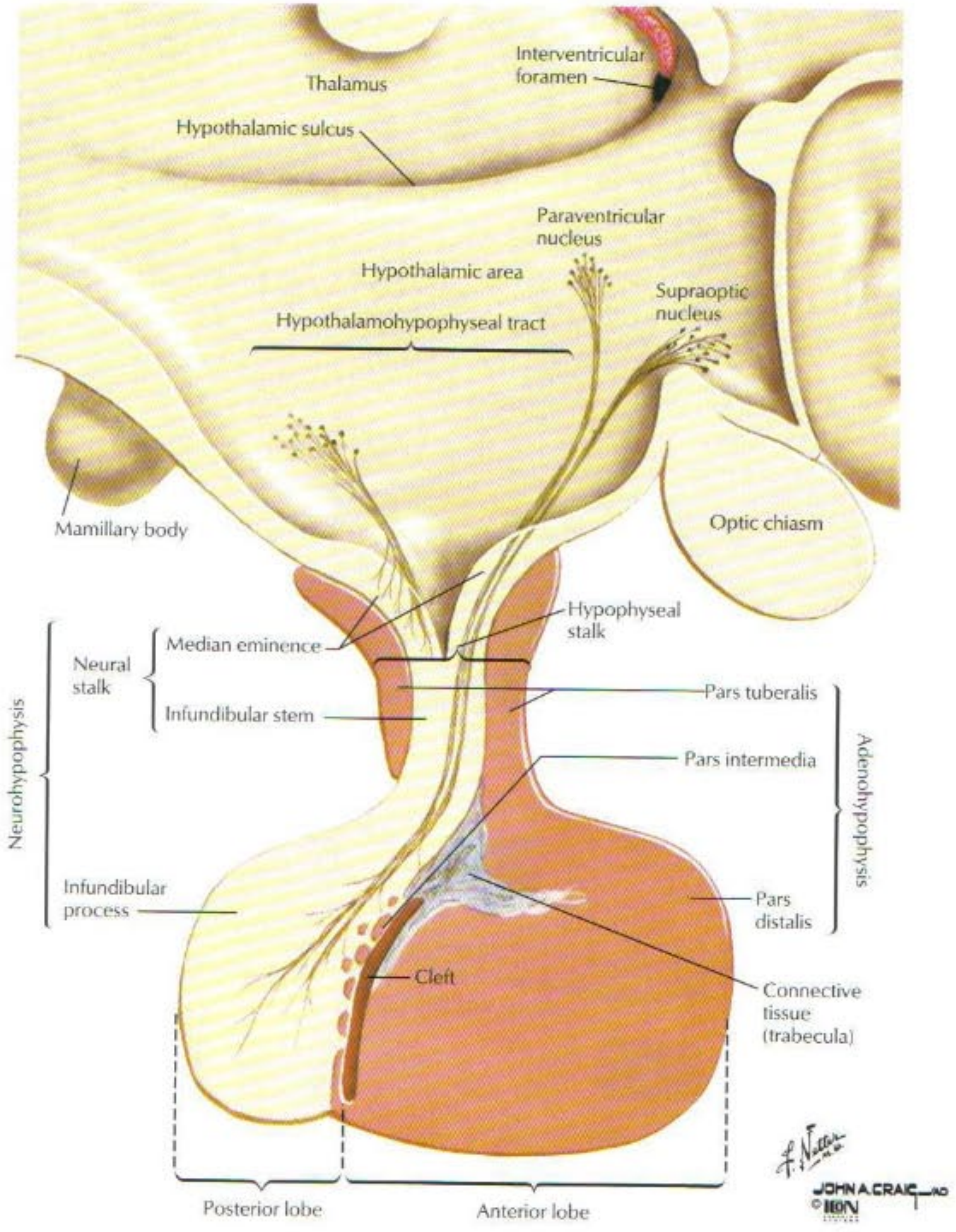
Thalamus
Interventricular foramen
Hypothalamic sulcus
Paraventricular nucleus
Hypothalamic area
Supraoptic nucleus
Hypothalamohypophyseal tract
Mamillary body
Optic chiasm
Hypophyseal stalk
Neural stalk
Median eminence
Infundibular stem
Pars tuberalis
Pars intermedia
Neurohypophysis
Adenohypophysis
Infundibular process
Pars distalis
Cleft
Connective tissue (trabecula)
Posterior lobe
Anterior lobe
F. Netter
JOHN A. CRAIG
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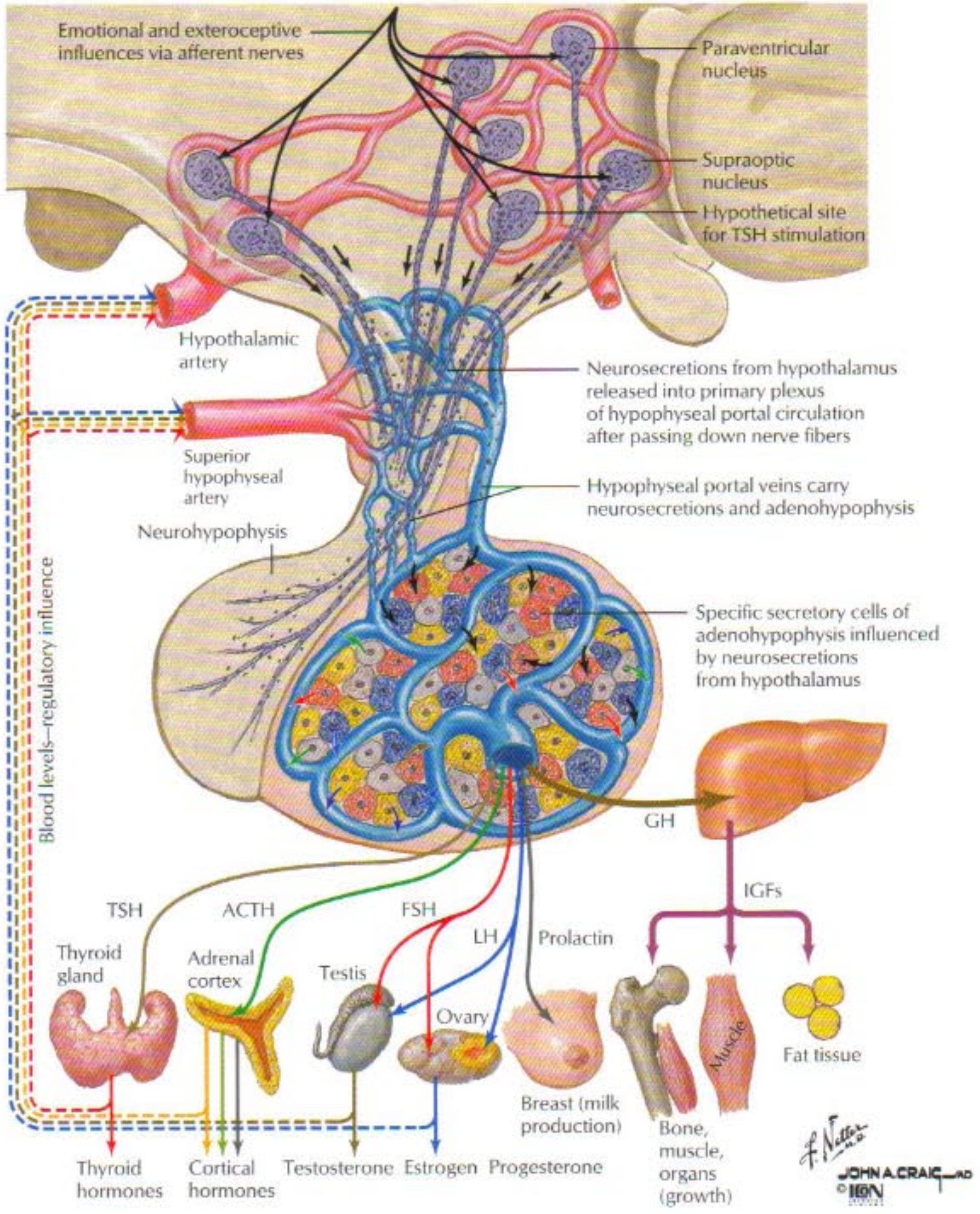
FIGURE 8.3 STRUCTURE OF HYPOTHALAMUS AND PITUITARY

The neurohypophysis (posterior pituitary) is formed as a downgrowth of the diencephalon of the brain. The adenohypophysis (anterior pituitary) is derived from Rathke's pouch (ectodermal tissue in the oropharynx). The intermediate lobe is not well developed in humans. Neuroendocrine cells in the hypothalamus send axons into the posterior pituitary and to the region of the median eminence. Hormones are released from these axons into the systemic blood (posterior pituitary) or into the hypothalamic-hypophyseal portal system (see Figure 8.4) in the region of the median eminence.


Emotional and exteroceptive influences via afferent nerves
Paraventricular nucleus
Supraoptic nucleus
Hypothetical site for TSH stimulation
Hypothalamic artery
Neurosecretions from hypothalamus released into primary plexus of hypophyseal portal circulation after passing down nerve fibers
Superior hypophyseal artery
Hypophyseal portal veins carry neurosecretions and adenohypophysis
Neurohypophysis
Blood levels—regulatory influence
Specific secretory cells of adenohypophysis influenced by neurosecretions from hypothalamus
GH
IGFs
TSH
ACTH
FSH
LH
Prolactin
Thyroid gland
Adrenal cortex
Testis
Ovary
Breast (milk production)
Muscle
Fat tissue
Bone, muscle, organs (growth)
Thyroid hormones
Cortical hormones
Testosterone
Estrogen
Progesterone
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JOHN A.CRAIG AD
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FIGURE 8.4 OVERVIEW OF ANTERIOR PITUITARY FUNCTION

Hypothalamic neuroendocrine cells release hormones into the hypothalamic-hypophyseal portal system that stimulate or inhibit the secretory cells of the anterior pituitary. Under the control of these hypothalamic releasing and inhibiting hormones, the cells of the anterior pituitary release tropic hormones, which then act on endocrine glands. The hormones secreted by the endocrine glands feed back on both the cells of the anterior pituitary and the hypothalamus to regulate the secretion of tropic hormones and releasing hormones.

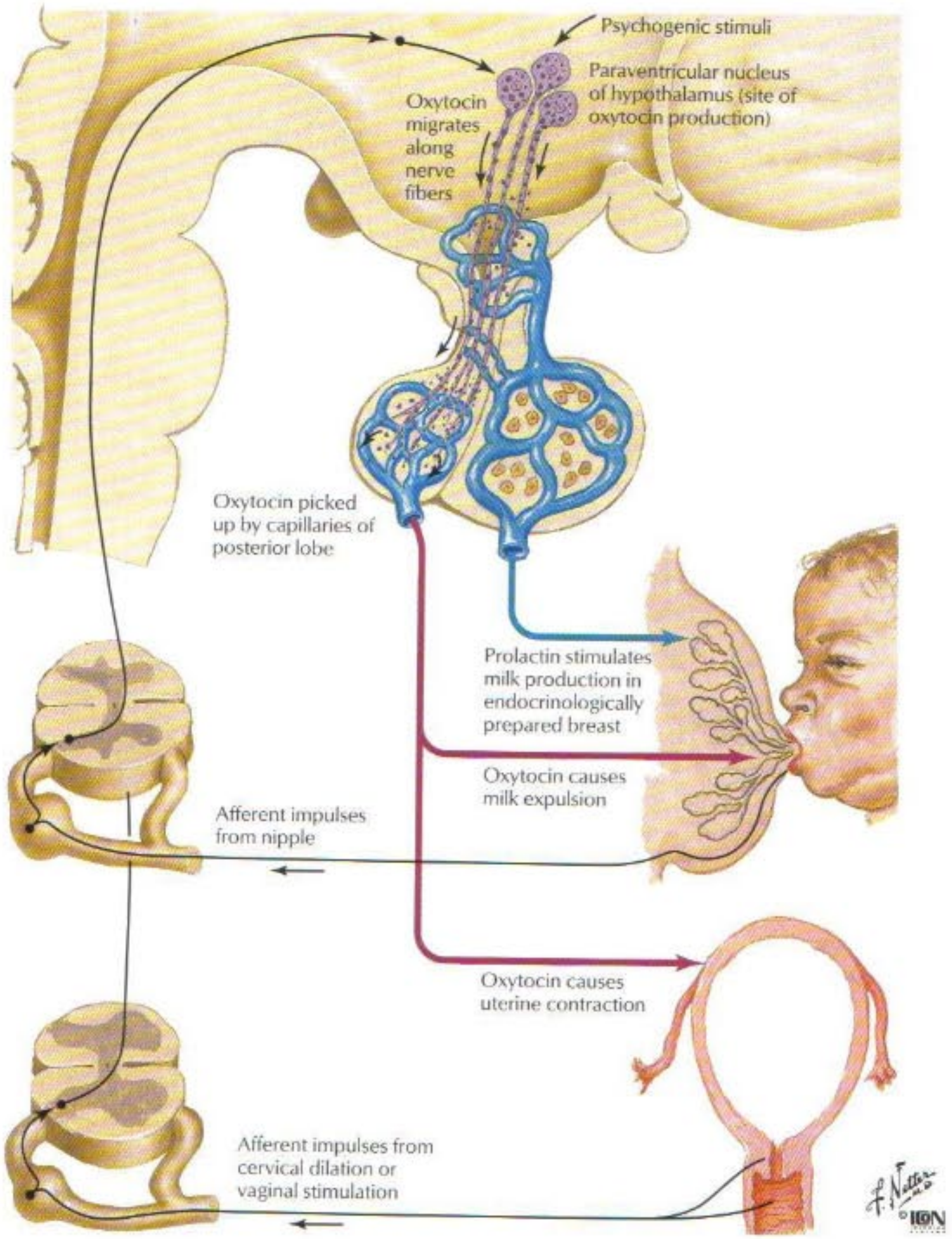
Psychogenic stimuli
Paraventricular nucleus of hypothalamus (site of oxytocin production)
Oxytocin migrates along nerve fibers
Oxytocin picked up by capillaries of posterior lobe
Prolactin stimulates milk production in endocrinologically prepared breast
Oxytocin causes milk expulsion
Afferent impulses from nipple
Oxytocin causes uterine contraction
Afferent impulses from cervical dilation or vaginal stimulation

FIGURE 8.5 POSTERIOR PITUITARY FUNCTION (OXYTOCIN)

Oxytocin is released from the posterior pituitary in response to vaginal stimulation and suckling. In response to vaginal stimulation, as occurs during sexual intercourse, oxytocin is released and causes uterine contraction. This may facilitate sperm transport through the uterus and uterine tubes. Oxytocin also facilitates childbirth by increasing uterine contractions during labor. During nursing, stimulation of the nipple by the suckling infant causes oxytocin release, which then acts on the myoepithelial cells surrounding the mammary gland alveoli and ducts causing expression of milk. Neural pathways activated during suckling also stimulate the secretion of prolactin.

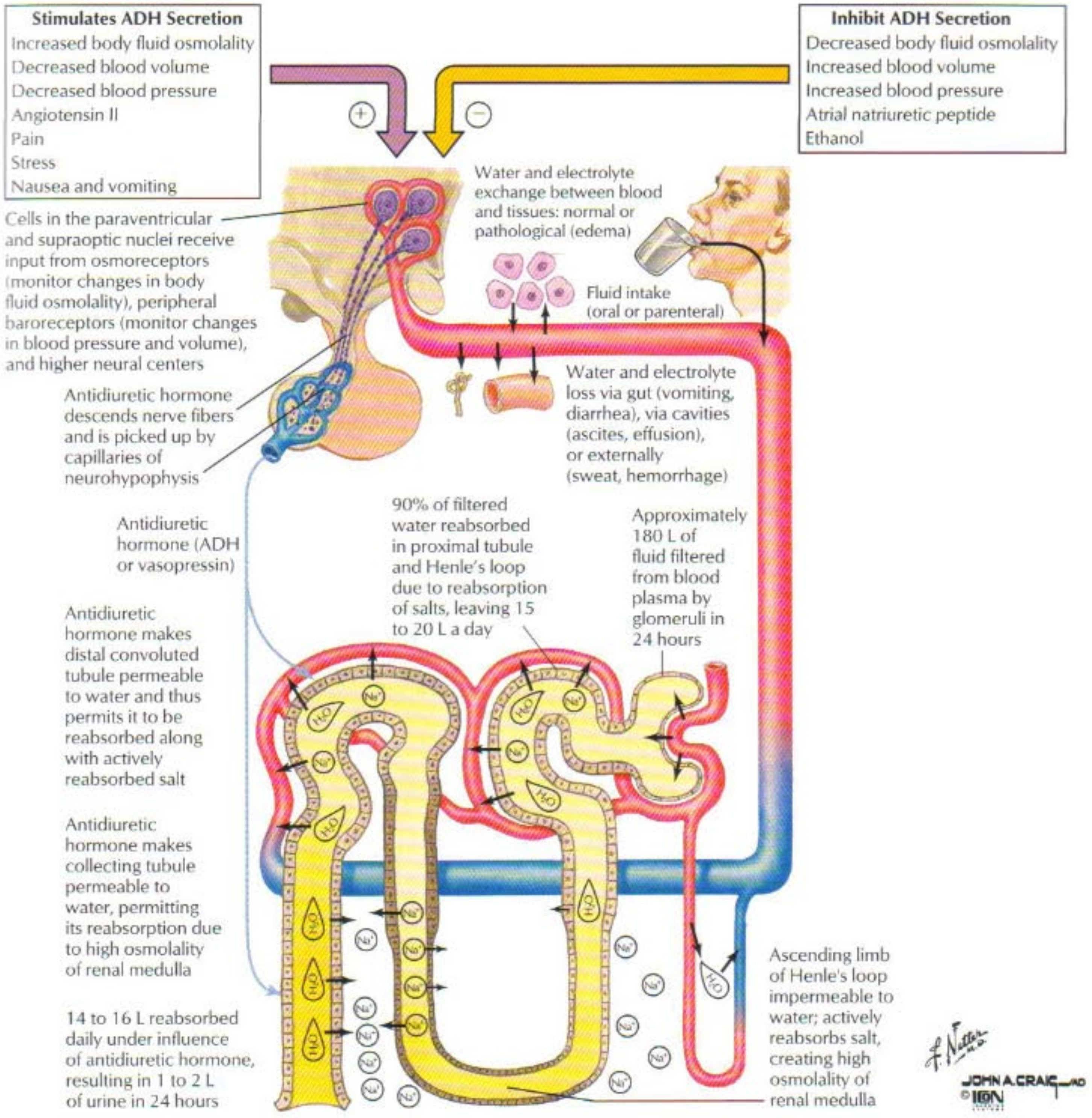
Stimulates ADH Secretion
Increased body fluid osmolality
Decreased blood volume
Decreased blood pressure
Angiotensin II
Pain
Stress
Nausea and vomiting
Inhibit ADH Secretion
Decreased body fluid osmolality
Increased blood volume
Increased blood pressure
Atrial natriuretic peptide
Ethanol
+
−
Cells in the paraventricular and supraoptic nuclei receive input from osmoreceptors (monitor changes in body fluid osmolality), peripheral baroreceptors (monitor changes in blood pressure and volume), and higher neural centers
Water and electrolyte exchange between blood and tissues: normal or pathological (edema)
Fluid intake (oral or parenteral)
Antidiuretic hormone descends nerve fibers and is picked up by capillaries of neurohypophysis
Water and electrolyte loss via gut (vomiting, diarrhea), via cavities (ascites, effusion), or externally (sweat, hemorrhage)
Antidiuretic hormone (ADH or vasopressin)
90% of filtered water reabsorbed in proximal tubule and Henle's loop due to reabsorption of salts, leaving 15 to 20 L a day
Approximately 180 L of fluid filtered from blood plasma by glomeruli in 24 hours
Antidiuretic hormone makes distal convoluted tubule permeable to water and thus permits it to be reabsorbed along with actively reabsorbed salt
Antidiuretic hormone makes collecting tubule permeable to water, permitting its reabsorption due to high osmolality of renal medulla
14 to 16 L reabsorbed daily under influence of antidiuretic hormone, resulting in 1 to 2 L of urine in 24 hours
Ascending limb of Henle's loop impermeable to water; actively reabsorbs salt, creating high osmolality of renal medulla
H_2O
Na^+
F. Netter M.D.
JOHN A.CRAIG_AD
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FIGURE 8.6 POSTERIOR PITUITARY FUNCTION (ADH)

Antidiuretic hormone (ADH), or vasopressin, is involved in the regulation of water balance. Changes in body fluid osmolality and blood volume and pressure are the primary physiologic regulators of ADH secretion (see also Figure 6.9). When ADH levels are elevated, a small volume of concentrated urine is excreted. When ADH levels are low, a large volume of dilute urine is excreted.

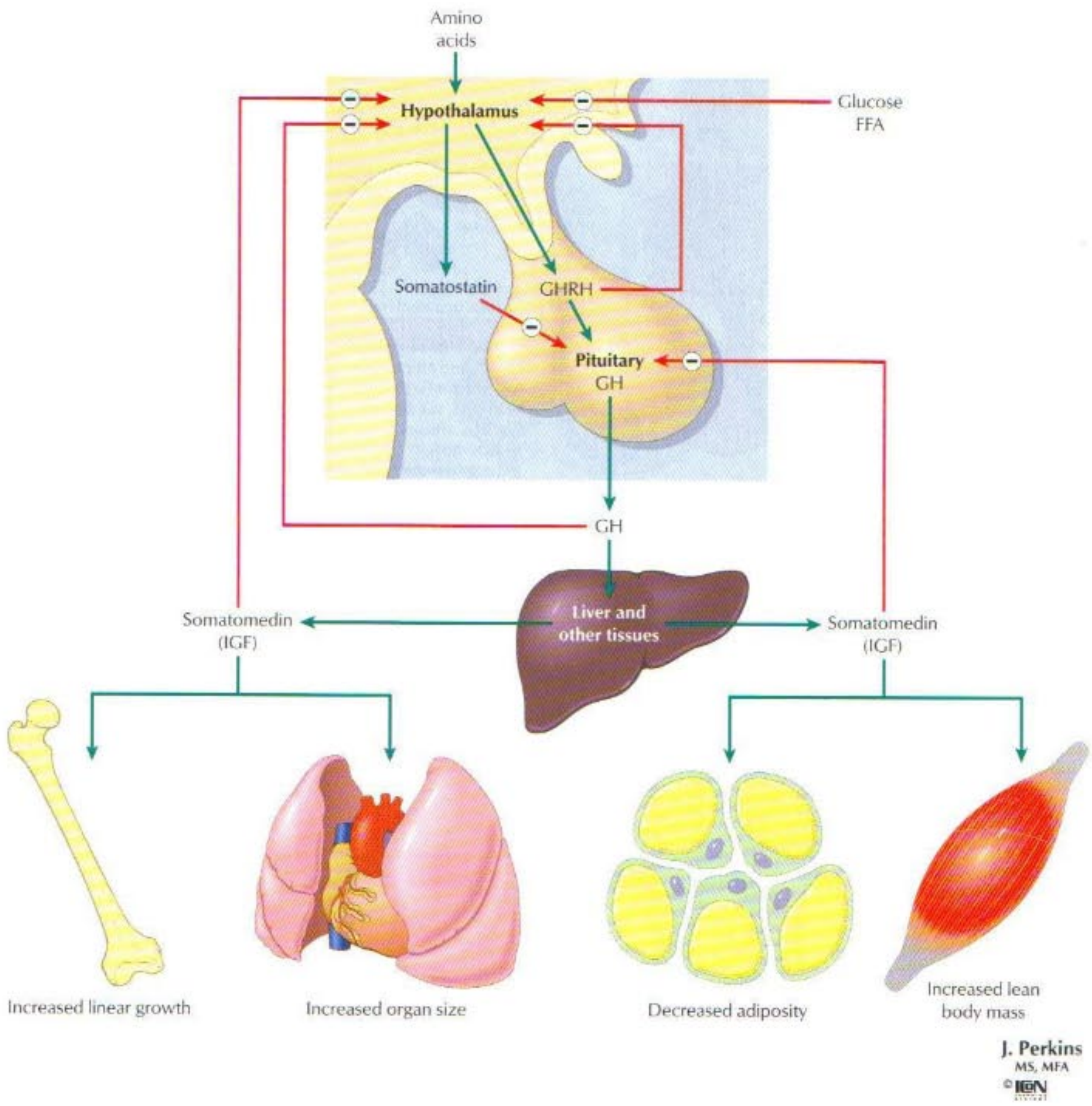
Amino acids
Hypothalamus
Glucose
FFA
Somatostatin
GHRH
Pituitary
GH
GH
Liver and other tissues
Somatomedin (IGF)
Somatomedin (IGF)
Increased linear growth
Increased organ size
Decreased adiposity
Increased lean body mass
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FIGURE 8.7 GROWTH HORMONE

Growth hormone's major physiological effect is to stimulate growth and development in children and adolescents. It also plays an important role in regulating overall body metabolism. Growth hormone produces many of effects through the generation, and then subsequent action of somatomedins such as insulin-like growth factor (IGF). Amino acids, glucose and FFA exert their effect on GH secretion via somatostatin. Amino acids inhibit somatostatin release (increase GH secretion) whereas glucose and FFA stimulate somatostatin release (inhibit GH secretion). *Abbreviations: FFA,* Free fatty acids; *GH,* growth hormone; *GHRH,* growth hormone–releasing hormone.

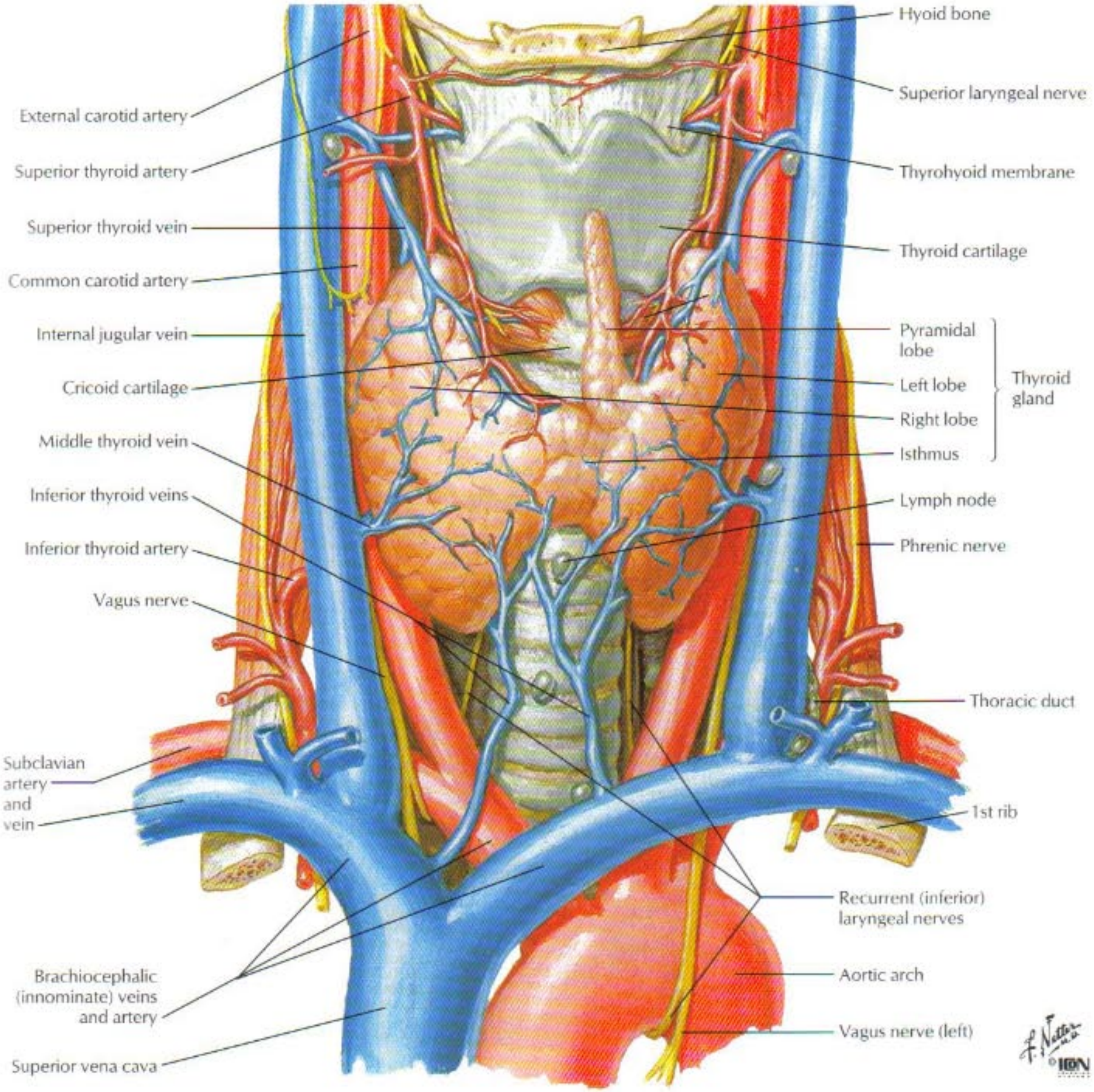
Hyoid bone
Superior laryngeal nerve
External carotid artery
Superior thyroid artery
Thyrohyoid membrane
Superior thyroid vein
Thyroid cartilage
Common carotid artery
Internal jugular vein
Pyramidal lobe
Cricoid cartilage
Left lobe
Right lobe
Isthmus
Thyroid gland
Middle thyroid vein
Inferior thyroid veins
Lymph node
Phrenic nerve
Inferior thyroid artery
Vagus nerve
Thoracic duct
Subclavian artery and vein
1st rib
Recurrent (inferior) laryngeal nerves
Brachiocephalic (innominate) veins and artery
Aortic arch
Vagus nerve (left)
Superior vena cava

FIGURE 8.8 THYROID GLAND STRUCTURE

The thyroid gland is a ductless endocrine gland that weighs about 20 grams and consists of a right and left lobe joined by an isthmus. In 15% of the population, there is a small pyramidal lobe extending cranially, as in this figure. The gland lies anterior to the trachea and just inferior to the cricoid cartilage. As with all endocrine glands, the thyroid has a rich vascular supply and venous drainage.

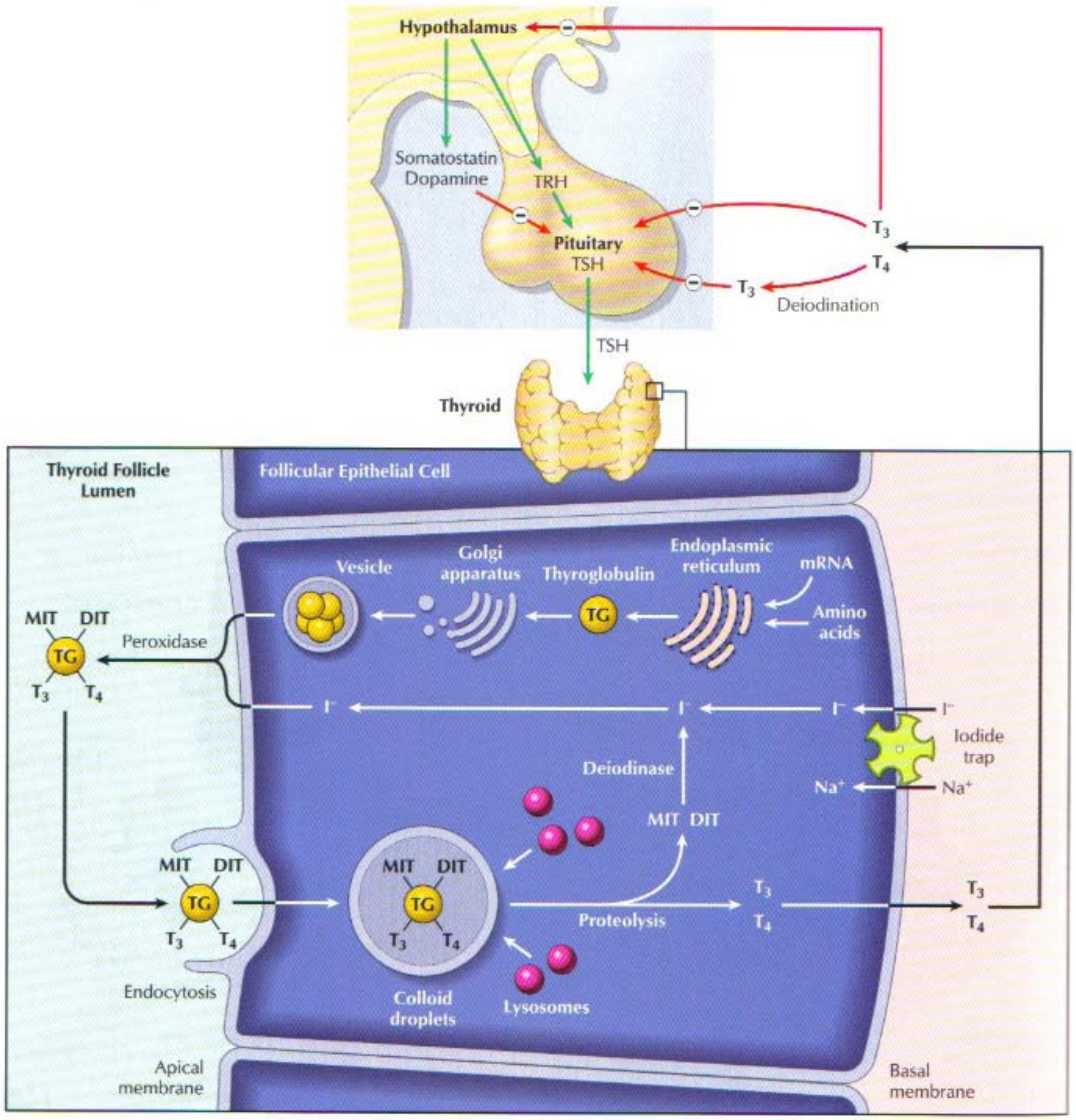
Hypothalamus
Somatostatin
Dopamine
TRH
Pituitary
TSH
T_3
T_4
T_3
Deiodination
TSH
Thyroid
Thyroid Follicle Lumen
Follicular Epithelial Cell
Vesicle
Golgi apparatus
Thyroglobulin
Endoplasmic reticulum
mRNA
Amino acids
TG
MIT DIT
Peroxidase
TG
T_3 T_4
I^-
I^-
I^-
I^-
Iodide trap
Deiodinase
Na^+
Na^+
MIT DIT
MIT DIT
TG
T_3 T_4
MIT DIT
TG
T_3 T_4
T_3
T_4
T_3
T_4
Proteolysis
Endocytosis
Colloid droplets
Lysosomes
Apical membrane
Basal membrane

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FIGURE 8.9 THYROID GLAND FUNCTION

The thyroid gland is composed of follicles formed by epithelial cells. These follicular epithelial cells synthesize, store, and secrete thyroxine (T_4) and triiodothyronine (T_3). The thyroid gland actively takes up iodide, iodinates tyrosine molecules (MIT = monoiodotyrosine; DIT = diiodotyrosine), couples these together to form T_4 and T_3, and stores these linked to thyroglobulin in the thyroid follicle. In the presence of thyroid-stimulating hormone (TSH), thyroglobulin is endocytosed and T_3 and T_4 are released into the blood (TSH also stimulates the synthesis of T_3, T_4, and thyroglobulin). Most of the secreted hormone (90%) is in the form of T_4, which serves as a prehormone, because T_4 is converted to the more active form T_3 by peripheral tissues.

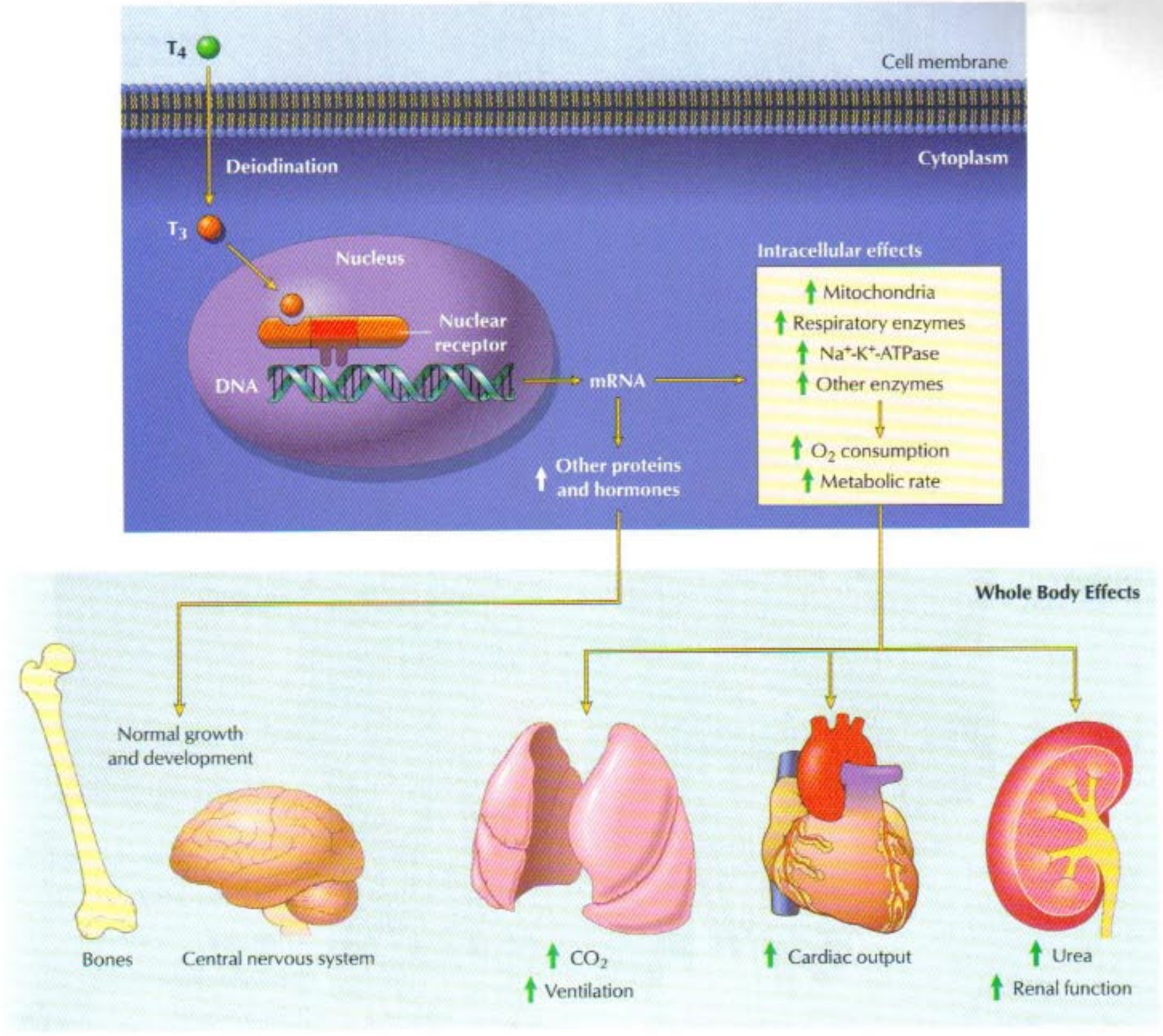
T4
Cell membrane
Cytoplasm
Deiodination
T3
Nucleus
Nuclear receptor
DNA
mRNA
↑ Other proteins and hormones
Intracellular effects
↑ Mitochondria
↑ Respiratory enzymes
↑ Na⁺-K⁺-ATPase
↑ Other enzymes
↑ O2 consumption
↑ Metabolic rate
Whole Body Effects
Normal growth and development
Bones
Central nervous system
↑ CO2
↑ Ventilation
↑ Cardiac output
↑ Urea
↑ Renal function

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Figure 8.10 Thyroid Hormone Action

Thyroxine (T_4) is converted to triiodothyronine (T_3) at target tissues. T_3 binds to a nuclear receptor, resulting in transcription of a host of cellular proteins and enzymes. The net effect is an increase in metabolic rate and O_2 consumption. These effects are associated with increased heart, lung, and kidney function. T_3 is also important for normal growth and development.

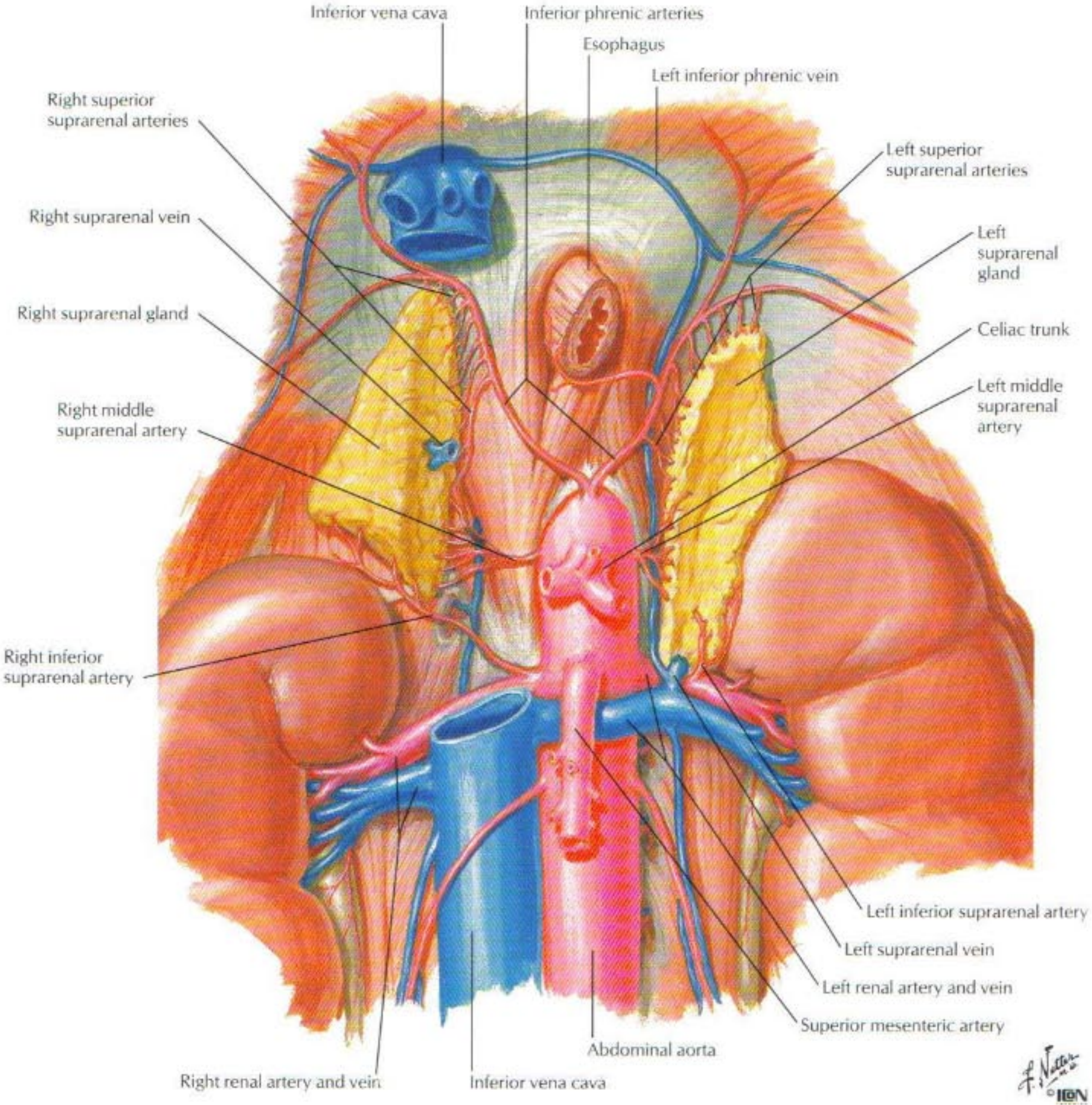
Inferior vena cava
Inferior phrenic arteries
Esophagus
Left inferior phrenic vein
Right superior suprarenal arteries
Left superior suprarenal arteries
Right suprarenal vein
Left suprarenal gland
Right suprarenal gland
Celiac trunk
Right middle suprarenal artery
Left middle suprarenal artery
Right inferior suprarenal artery
Left inferior suprarenal artery
Left suprarenal vein
Left renal artery and vein
Superior mesenteric artery
Abdominal aorta
Right renal artery and vein
Inferior vena cava
F. Netter
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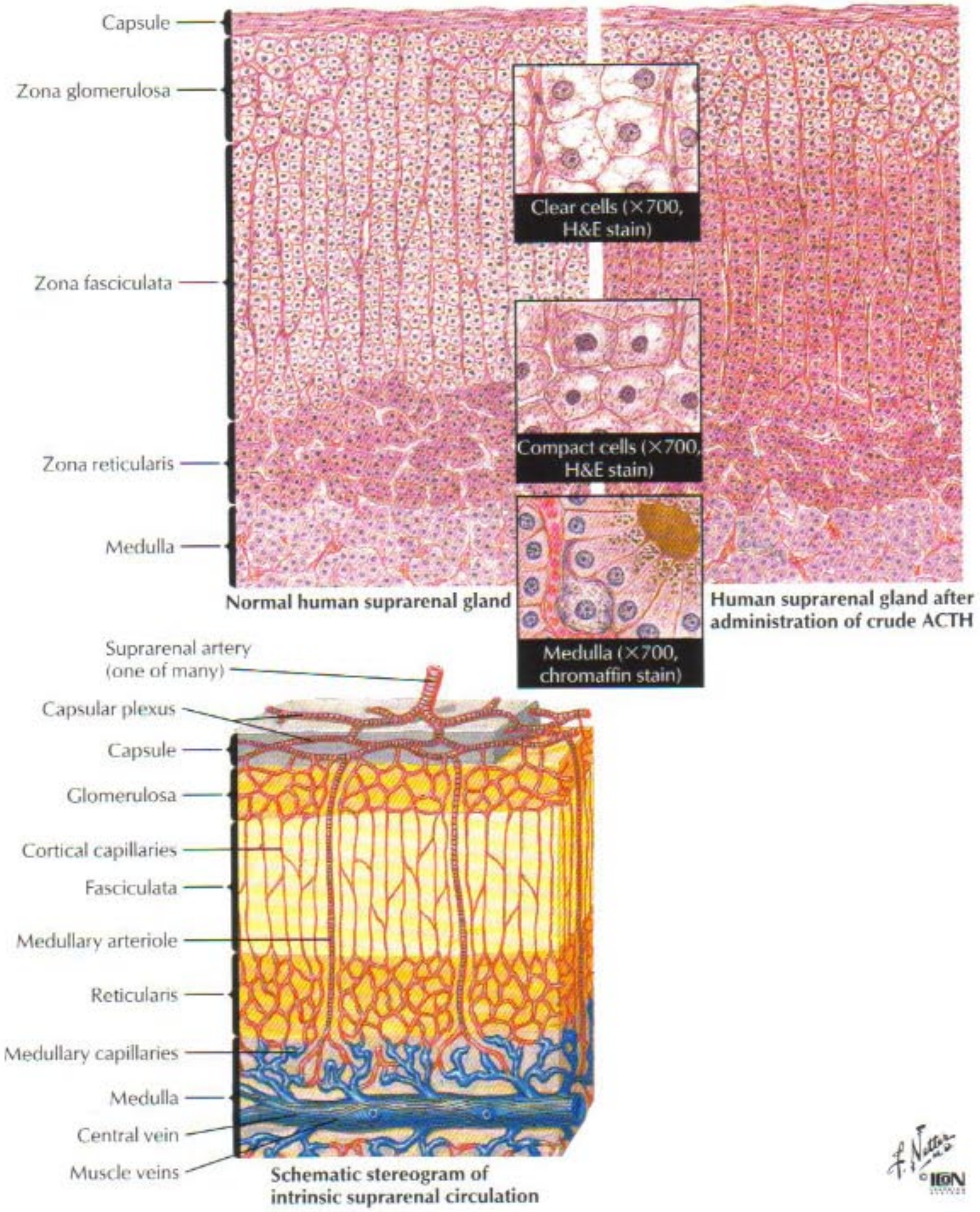
Figure 8.11 Adrenal Gland Structure

The paired adrenal (suprarenal) glands are retroperitoneal ductless endocrine glands that are nestled above the superior pole of each kidney and the overlying diaphragm. Each gland normally weighs about 7 to 8 grams, is highly vascularized, and consists of an outer cortex and an inner medulla (see Figure 8.12).


Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Clear cells (×700, H&E stain)
Compact cells (×700, H&E stain)
Medulla (×700, chromaffin stain)
Suprarenal artery (one of many)
Capsular plexus
Capsule
Glomerulosa
Cortical capillaries
Fasciculata
Medullary arteriole
Reticularis
Medullary capillaries
Medulla
Central vein
Muscle veins
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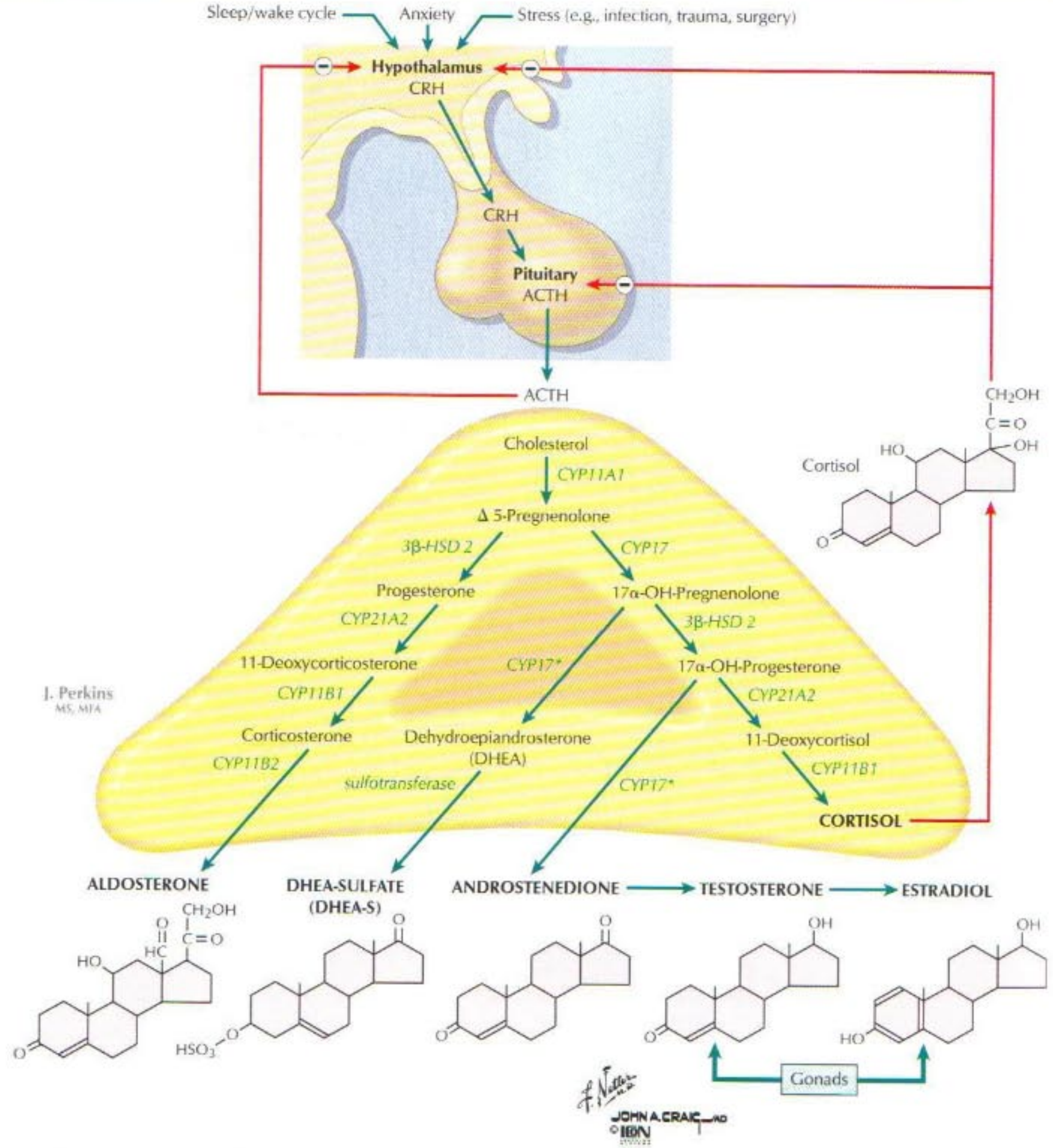
Normal human suprarenal gland

Human suprarenal gland after administration of crude ACTH

Schematic stereogram of intrinsic suprarenal circulation

FIGURE 8.12 ADRENAL GLAND HISTOLOGY

The adrenal gland consists of a cortex and medulla, and both regions are richly vascularized by a radially oriented plexus of vessels. The adrenal cortex produces more than two dozen steroid hormones and structurally is divided into three distinct histological regions: an outer zona glomerulosa that produces mineralocorticoids (principally aldosterone), a middle zona fasciculata that produces glucocorticoids (primarily cortisol, corticosterone, and cortisone), and an inner zona reticularis that produces androgens. As shown in this figure, ACTH stimulation significantly affects the maintenance and function of the inner two layers of the adrenal cortex. The adrenal medulla occupies the center of the adrenal gland and produces epinephrine and norepinephrine. The medullary cells actually are the postganglionic elements of the sympathetic division of the autonomic nervous system, but as endocrine cells, they release epinephrine and norepinephrine into the blood rather than into a synaptic cleft. Epinephrine accounts for about 70% to 80% of the medullary secretions. As illustrated in the lower panel, blood drains from the cortex into the medulla. This vascular arrangement ensures that the medulla receives large amounts of cortisol, which stimulates the enzyme that converts norepinephrine to epinephrine (i.e., phenylethanolamine-*N*-methyltransferase).


Sleep/wake cycle
Anxiety
Stress (e.g., infection, trauma, surgery)
Hypothalamus
CRH
CRH
Pituitary
ACTH
ACTH
Cholesterol
CYP11A1
Δ 5-Pregnenolone
3β-HSD 2
CYP17
Progesterone
17α-OH-Pregnenolone
CYP21A2
3β-HSD 2
11-Deoxycorticosterone
CYP17*
17α-OH-Progesterone
CYP11B1
CYP21A2
Corticosterone
Dehydroepiandrosterone (DHEA)
11-Deoxycortisol
CYP11B2
sulfotransferase
CYP17*
CYP11B1
CORTISOL
Cortisol
ALDOSTERONE
DHEA-SULFATE (DHEA-S)
ANDROSTENEDIONE
TESTOSTERONE
ESTRADIOL
Gonads
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JOHN A.CRAIG AD
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FIGURE 8.13 ADRENAL CORTICAL HORMONES

The adrenal cortex synthesizes and secretes glucocorticoid hormones (e.g., cortisol), mineralocorticoid hormones (e.g., aldosterone), and androgens (e.g., DHEA, androstenedione). Small amounts of circulating testosterone and estradiol are derived from the adrenal cortex, but the gonads are their primary source. All of the adrenal steroid hormones are derived from cholesterol. Cortisol secretion is under the control of adrenocorticotropic hormone (ACTH), which is secreted from the anterior pituitary in response to corticotropin-releasing hormone. ACTH also stimulates the production of adrenal androgens. ACTH is not the primary regulator of aldosterone secretion (see Figure 8.16). *Abbreviations: CYP11A1*, Side-chain cleavage; *3β-HSD 2*, 3β-hydroxysteroid dehydrogenase; *CYP21A2*, 21-hydroxylase; *CYP11B1*, 11β-hydroxylase; *CYP11B2*, aldosterone synthetase; *CYP17*, 17α-hydroxylase; *CTP17**, 17,20-lyase.

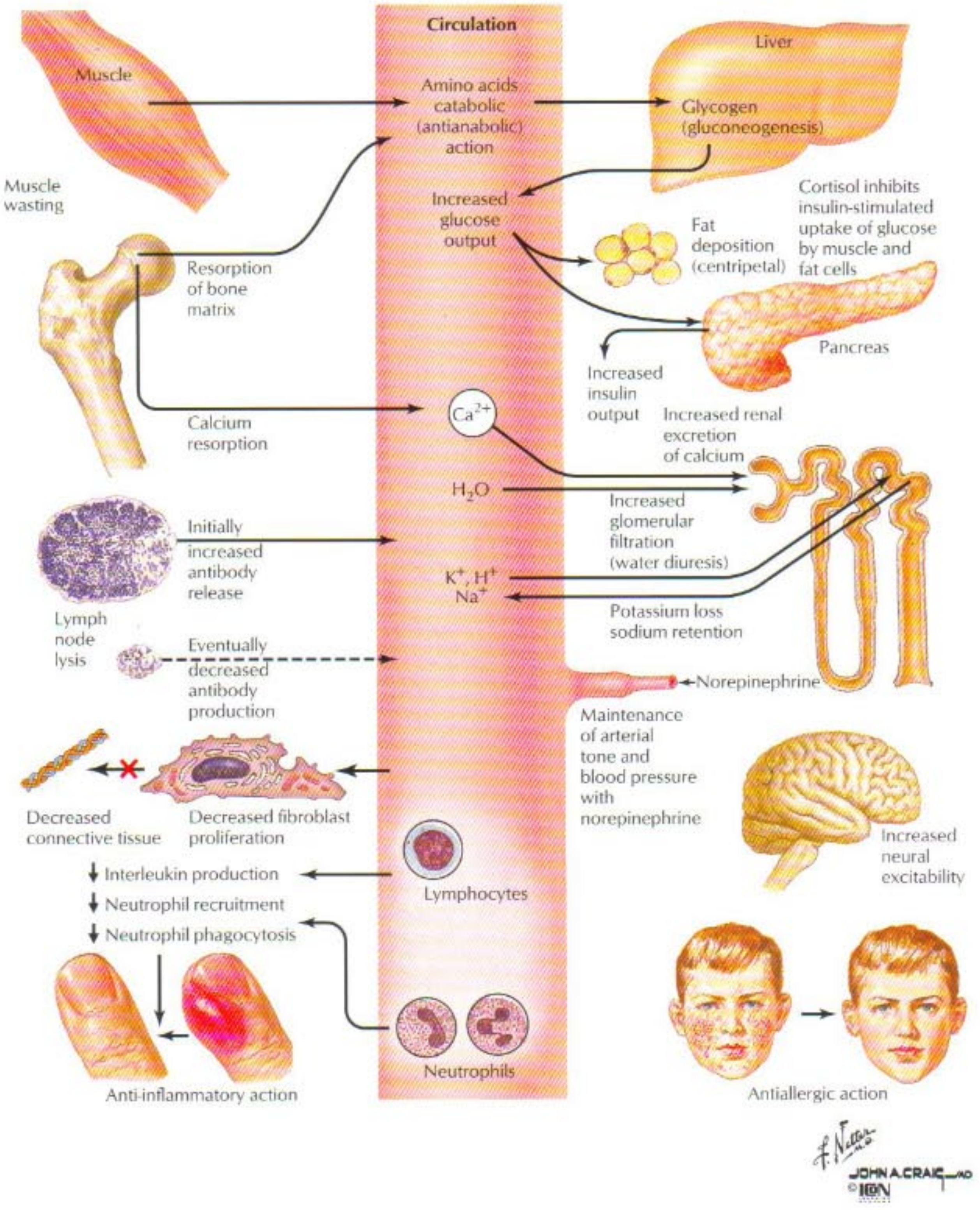
Circulation
Muscle
Muscle wasting
Amino acids catabolic (antianabolic) action
Liver
Glycogen (gluconeogenesis)
Increased glucose output
Fat deposition (centripetal)
Cortisol inhibits insulin-stimulated uptake of glucose by muscle and fat cells
Pancreas
Increased insulin output
Resorption of bone matrix
Calcium resorption
Ca^{2+}
Increased renal excretion of calcium
H_2O
Increased glomerular filtration (water diuresis)
Initially increased antibody release
K^+, H^+
Na^+
Potassium loss sodium retention
Lymph node lysis
Eventually decreased antibody production
Norepinephrine
Maintenance of arterial tone and blood pressure with norepinephrine
Decreased connective tissue
Decreased fibroblast proliferation
Increased neural excitability
↓ Interleukin production
↓ Neutrophil recruitment
↓ Neutrophil phagocytosis
Lymphocytes
Neutrophils
Anti-inflammatory action
Antiallergic action
F. Netter M.D.
JOHN A.CRAIG MD
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FIGURE 8.14 ACTIONS OF CORTISOL

Cortisol has many direct and indirect actions. It causes muscle wasting, fat deposition, hyperglycemia, insulin resistance, osteoporosis, suppression of the immune response (anti-inflammatory), and reduced production of connective tissue that can lead to poor wound healing. At high levels, it can exhibit mineralocorticoid actions and cause Na^+ retention and enhanced K^+ and H^+ excretion by the kidneys. Cortisol is also necessary for the normal production of epinephrine by the adrenal medulla (see Figure 8.17).

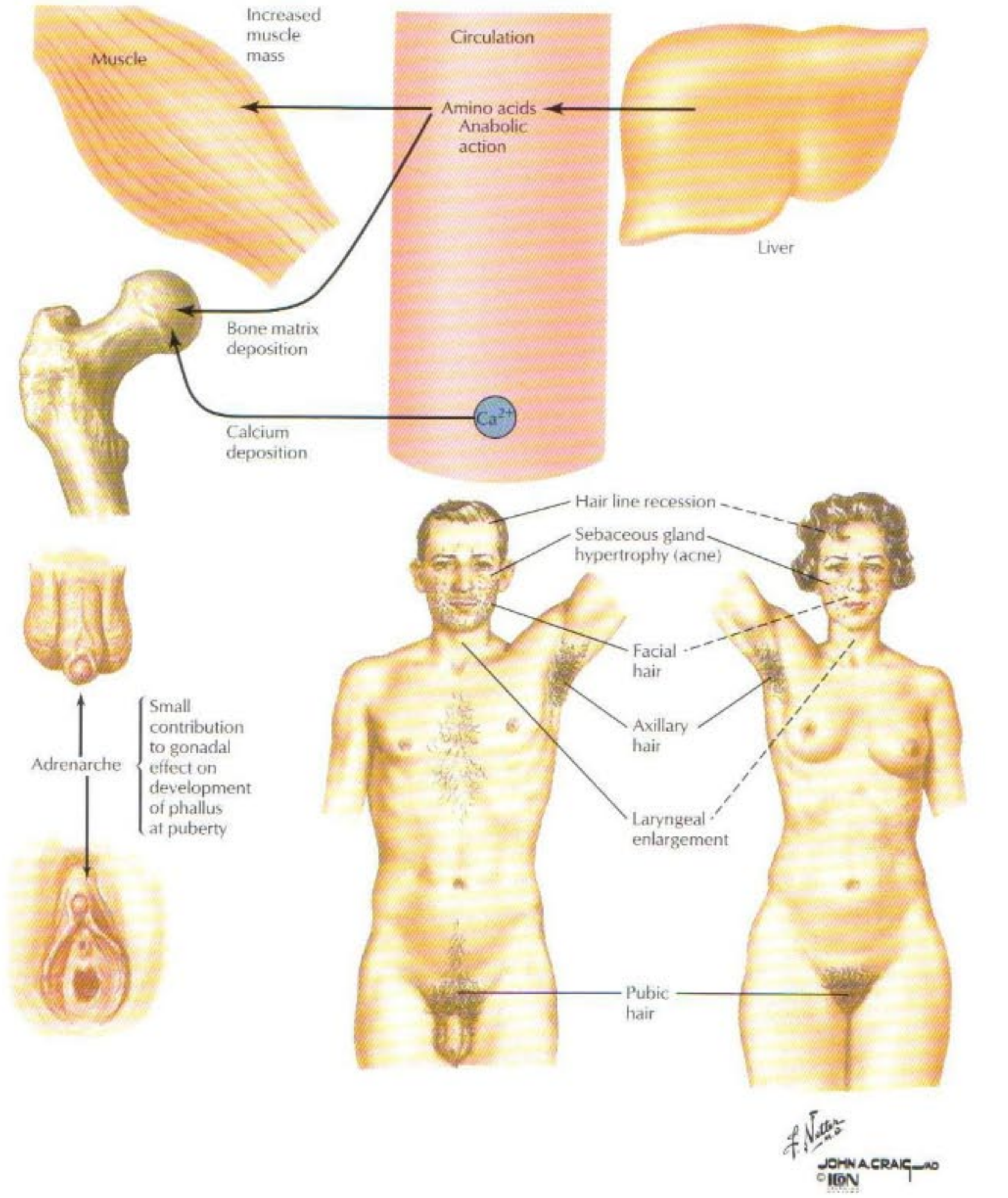
Increased muscle mass
Muscle
Circulation
Amino acids
Anabolic action
Liver
Bone matrix deposition
Calcium deposition
Ca^{2+}
Hair line recession
Sebaceous gland hypertrophy (acne)
Facial hair
Axillary hair
Laryngeal enlargement
Pubic hair
Adrenarche
Small contribution to gonadal effect on development of phallus at puberty
F. Netter M.D.
JOHN A. CRAIG—AD
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FIGURE 8.15 ACTIONS OF ADRENAL ANDROGENS

The adrenal androgens, dehydroepiandrosterone (DHEA) and androstenedione, do not have major effects in males, where the actions of testosterone predominate. In females, the adrenal glands are the primary source of circulating androgens. These adrenal androgens are responsible for the growth of both pubic and axillary hair. In both sexes, adrenal androgens play an important role in puberty. In early puberty, the adrenal androgens contribute to development of the external genitalia and other secondary sexual characteristics—a process termed adrenarche (see Figure 8.25). The general effects of androgens are anabolic, leading to increased muscle mass and bone formation. They also cause sebaceous gland hypertrophy, hairline recession, and growth of facial hair.

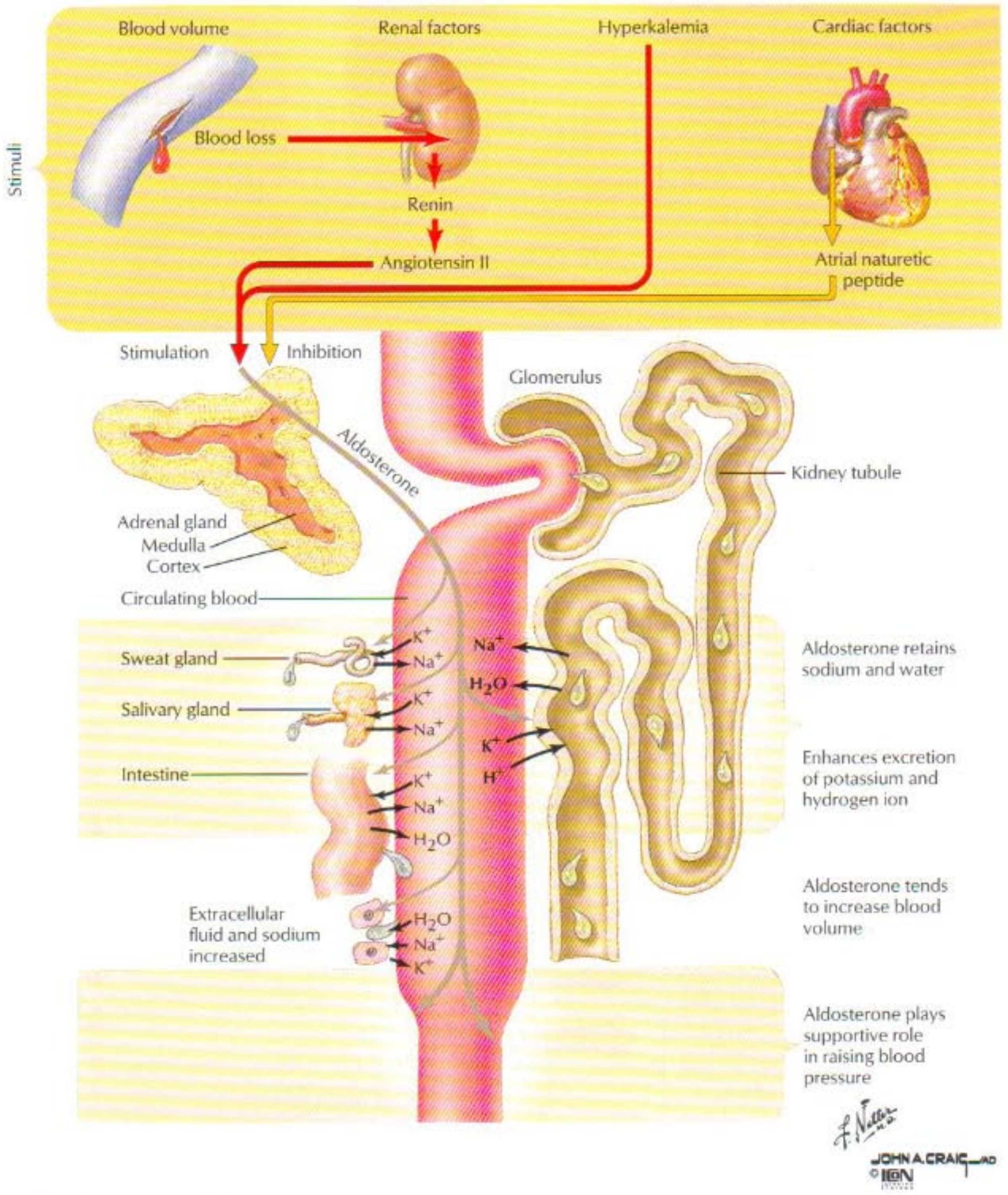
Stimuli
Blood volume
Renal factors
Hyperkalemia
Cardiac factors
Blood loss
Renin
Angiotensin II
Atrial naturetic peptide
Stimulation
Inhibition
Glomerulus
Aldosterone
Kidney tubule
Adrenal gland
Medulla
Cortex
Circulating blood
Sweat gland
Salivary gland
Intestine
K^+
Na^+
H_2O
H^+
Extracellular fluid and sodium increased
Aldosterone retains sodium and water
Enhances excretion of potassium and hydrogen ion
Aldosterone tends to increase blood volume
Aldosterone plays supportive role in raising blood pressure
F. Netter M.D.
JOHN A.CRAIG AD
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FIGURE 8.16 ACTIONS OF ALDOSTERONE

The mineralocorticoid aldosterone plays an important role in regulating the extracellular fluid (ECF) and blood volumes and in maintaining K^+ balance. When ECF and blood volumes are reduced (e.g., hemorrhage, diarrhea), renin is released from the kidney, which in turn increases angiotensin II levels. Angiotensin II is a potent stimulator of aldosterone secretion by the adrenal gland. Aldosterone acts on a number of organs, causing the retention of Na^+ and water, a response that serves to increase ECF and blood volume. The kidney is the most important organ in this response (see Figures 6.12 and 6.14). When the ECF and blood volumes are increased (e.g., congestive heart failure), atrial natriuretic peptide is secreted and acts on the adrenal cortex to inhibit aldosterone secretion (see Figure 6.13). An increase in the $[K^+]$ of the ECF (hyperkalemia) also stimulates aldosterone secretion by the adrenal cortex. Aldosterone acts primarily on the kidney to stimulate K^+ excretion (see Figure 6.15). Finally, aldosterone increases urinary H^+ excretion (see Figure 6.17).

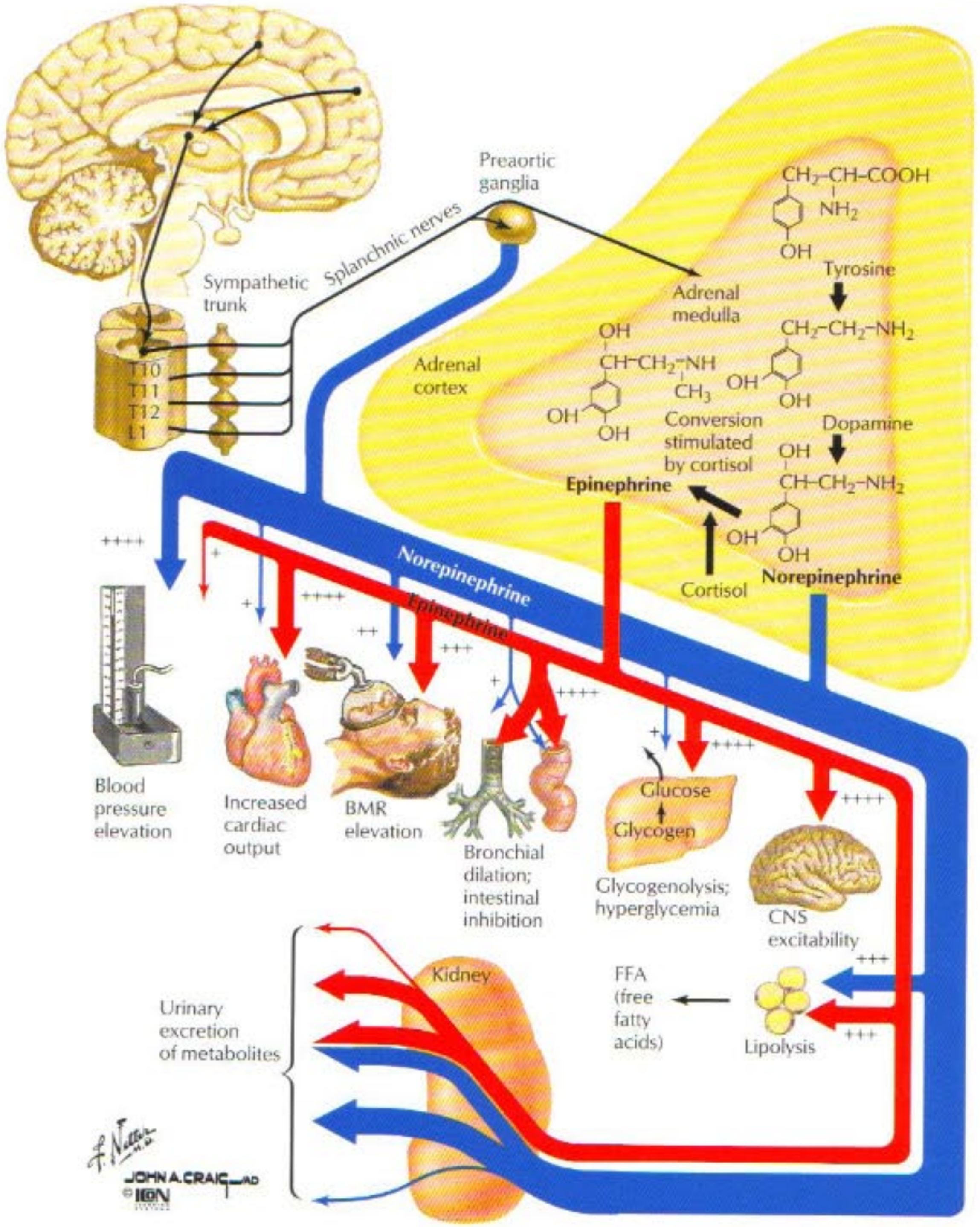
Preaortic ganglia
Splanchnic nerves
Sympathetic trunk
T10
T11
T12
L1
Adrenal cortex
Adrenal medulla
Tyrosine
Dopamine
Norepinephrine
Epinephrine
Conversion stimulated by cortisol
Cortisol
Norepinephrine
Epinephrine
++++
+
+
++++
++
+++
+
++++
+
++++
++++
+++
+++
Blood pressure elevation
Increased cardiac output
BMR elevation
Bronchial dilation; intestinal inhibition
Glucose
Glycogen
Glycogenolysis; hyperglycemia
CNS excitability
FFA (free fatty acids)
Lipolysis
Kidney
Urinary excretion of metabolites
F. Netter
JOHN A. CRAIG
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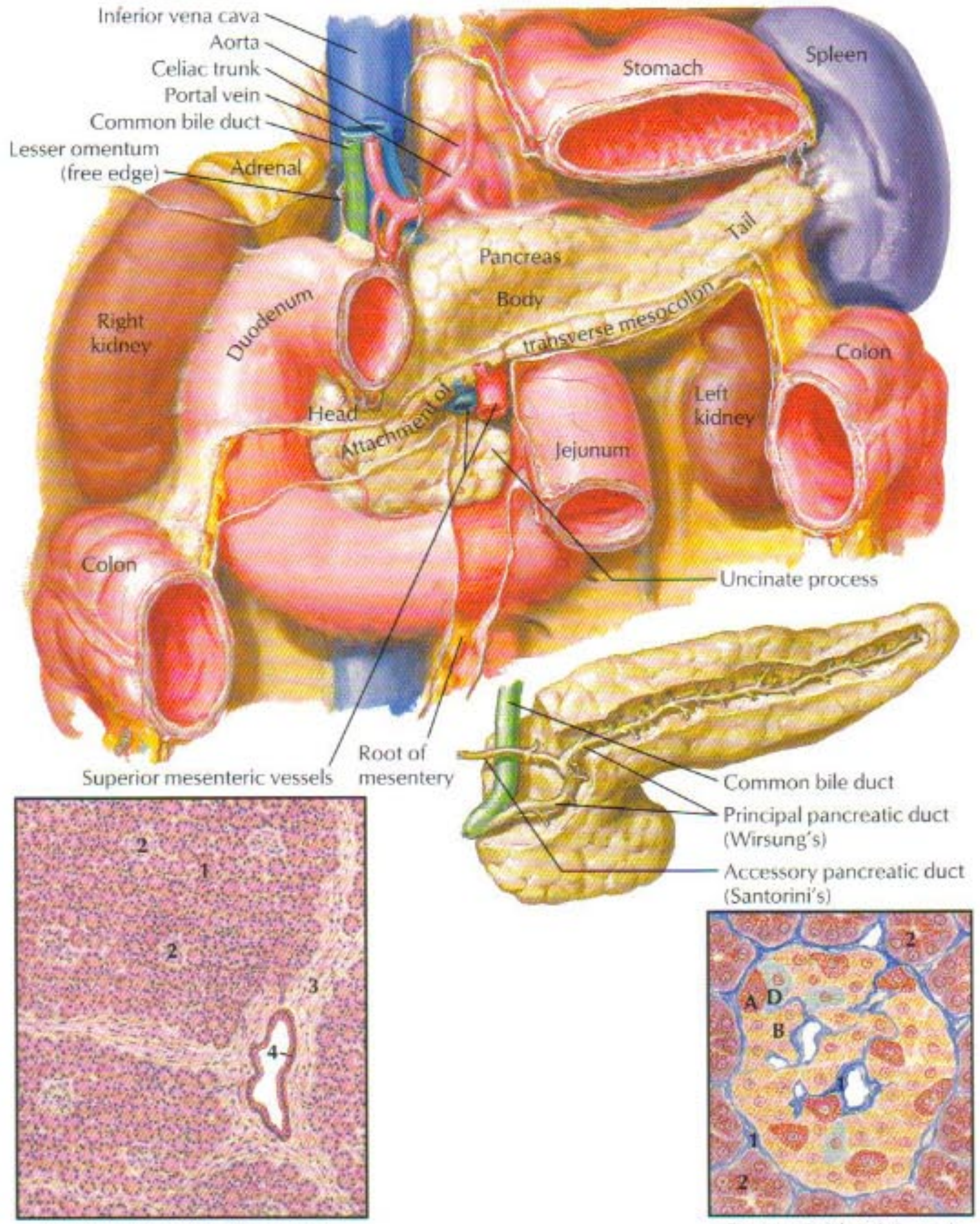
FIGURE 8.17 FUNCTION OF THE ADRENAL MEDULLA

The adrenal medulla produces epinephrine and norepinephrine. The medullary cells actually are the postganglionic elements of the sympathetic division of the autonomic nervous system, but as endocrine cells, they release epinephrine and norepinephrine into the blood rather than into a synaptic cleft. Epinephrine accounts for about 70% to 80% of the medullary secretions. The relative magnitude and effects of epinephrine and norepinephrine are illustrated.

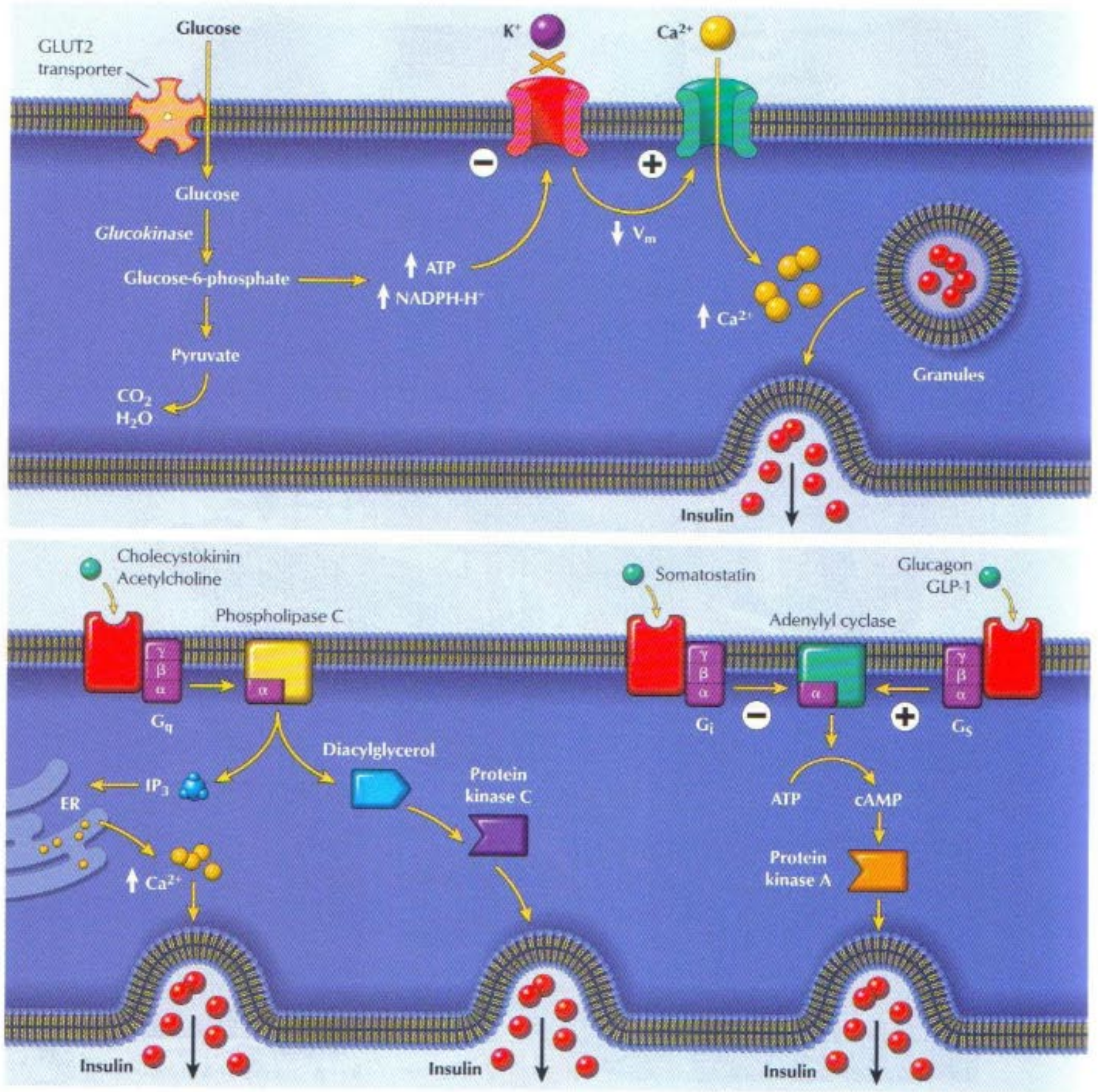

Inferior vena cava
Aorta
Celiac trunk
Portal vein
Common bile duct
Lesser omentum (free edge)
Adrenal
Stomach
Spleen
Tail
Pancreas
Body
Transverse mesocolon
Duodenum
Right kidney
Head
Attachment of
Jejunum
Left kidney
Colon
Colon
Uncinate process
Superior mesenteric vessels
Root of mesentery
Common bile duct
Principal pancreatic duct (Wirsung's)
Accessory pancreatic duct (Santorini's)
1
2
2
3
4
2
A
D
B
1
1
2

Low-power section of pancreas
1. Acini, **2.** islet, **3.** interlobular septum, **4.** interlobular duct

Pancreatic islet: **A** (=α−), **B** (=β−), and **D** (=δ−) cells.
1. Reticulum, **2.** acini

FIGURE 8.18 STRUCTURE OF THE ENDOCRINE PANCREAS

The pancreas is both an exocrine and endocrine gland. Its digestive enzymes are secreted into the duodenum via the pancreatic duct system, and about 99% of the cells are exocrine in function (see Figures 7.26 and 7.27). The endocrine portion of the pancreas is represented by clusters of islet cells (of Langerhans) (lower left micrograph), a heterogeneous population of cells responsible for the elaboration and secretion of glucagon (α-cells), insulin (β-cells), and somatostatin (δ-cells). Glucagon is a fuel-mobilization hormone (see Figure 8.21). Insulin is a fuel-storage hormone (see Figure 8.20). Somatostatin has a number of actions in the GI tract; within the islets, it acts on both the α- and β-cells to suppress glucagon and insulin secretion. A fourth cell type, the F cell (not shown), secretes pancreatic polypeptide, whose primary action is to inhibit the secretion of enzymes and HCO_3^- by the exocrine component of the pancreas.


Glucose
GLUT2 transporter
K^+
Ca^{2+}
Glucose
Glucokinase
Glucose-6-phosphate
↑ ATP
↑ NADPH-H^+
↓ V_m
↑ Ca^{2+}
Pyruvate
CO_2
H_2O
Granules
Insulin
Cholecystokinin
Acetylcholine
Phospholipase C
γ
β
α
G_q
Diacylglycerol
Protein kinase C
IP_3
ER
↑ Ca^{2+}
Somatostatin
Adenylyl cyclase
Glucagon
GLP-1
G_i
G_s
ATP
cAMP
Protein kinase A
Insulin
Insulin
Insulin

J. Perkins
MS, MFA
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FIGURE 8.19 INSULIN SECRETION

The most important factor regulating insulin secretion is the glucose concentration of the blood. When the blood glucose concentration increases, insulin secretion is stimulated. Glucose enters the cell, where its metabolism increases intracellular ATP levels. The increased ATP levels close an ATP-dependent K^+ channel in the plasma membrane and thereby depolarize the membrane potential (V_m). This membrane potential depolarization opens voltage-sensitive Ca^{2+} channels, and the intracellular [Ca^{2+}] increases. The rise in intracellular [Ca^{2+}] triggers exocytosis of the insulin-containing secretory granules. Other factors potentiate this effect of glucose on insulin secretion. Hormones and candidate hormones released by neuroendocrine cells in the intestine during digestion facilitate insulin secretion. These hormones and candidate hormones include cholecystokinin, glucagon-like peptide (GLP-1) and glucagon. Acetylcholine (from vagal efferents) also stimulates insulin secretion, while somatostatin from the islet δ-cells inhibits secretion.

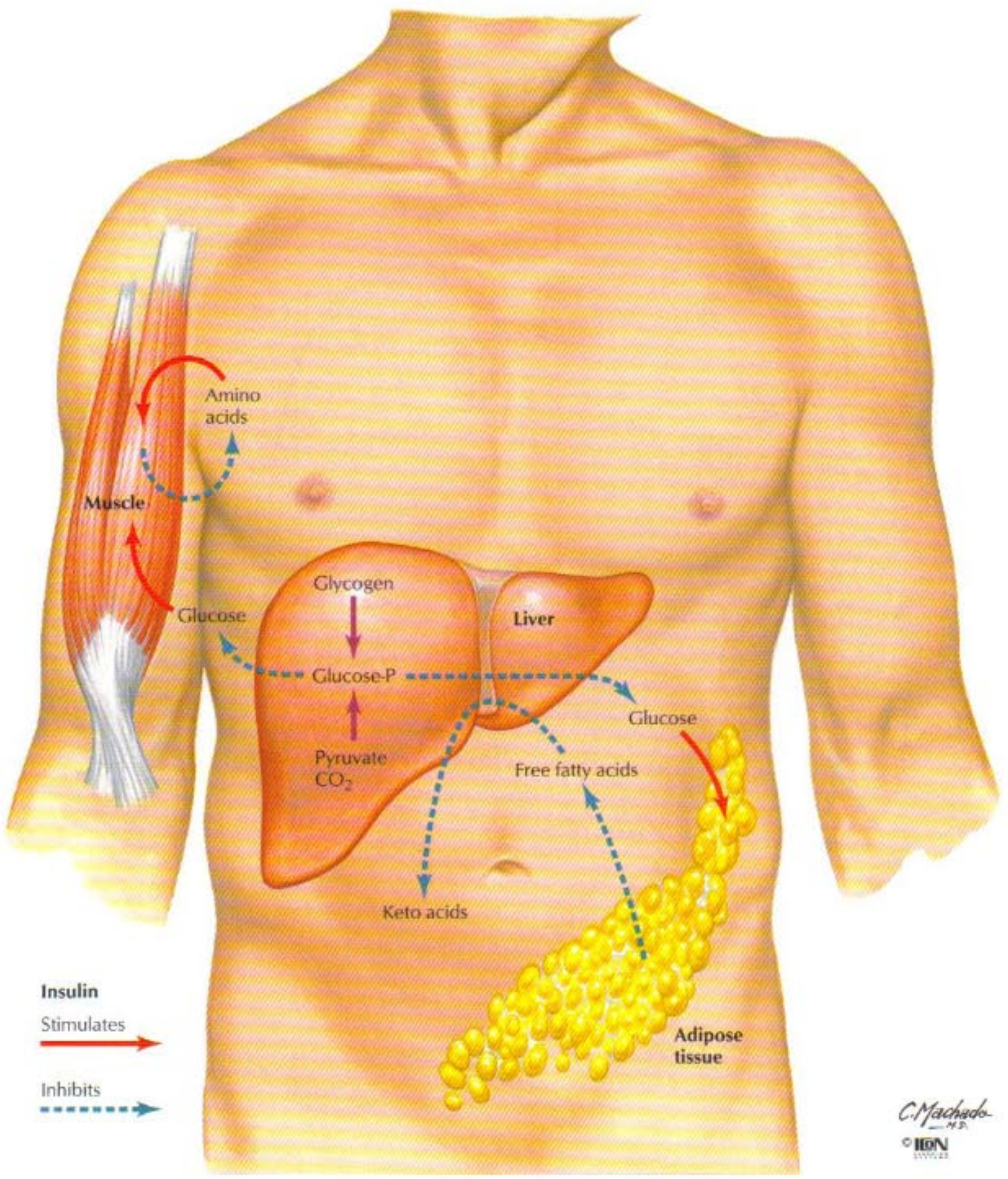
Amino acids
Muscle
Glycogen
Liver
Glucose
Glucose-P
Glucose
Pyruvate
CO_2
Free fatty acids
Keto acids
Insulin
Stimulates
Inhibits
Adipose tissue
C.Machado M.D.
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Figure 8.20 ACTIONS OF INSULIN

Insulin is a fuel-storage hormone. The major fuels used by cells are glucose, fatty acids, and keto acids (derived during fatty acid metabolism). Some cells preferentially use glucose as their fuel (e.g., neurons), whereas other cells preferentially use fatty acids (e.g., skeletal muscle). Keto acids can be used by many cells when glucose and fatty acids are not readily available (e.g., fasting). Insulin stimulates the uptake of glucose into cells, where it is stored in the form of glycogen (especially in the liver and skeletal muscle). It also stimulates fat synthesis and inhibits lipolysis, thus storing fatty acids as triglycerides (fatty acid metabolism to keto acids is also inhibited). Finally, insulin stimulates the uptake of amino acids into cells and their storage as protein. The net effect is that blood levels of glucose and keto acids decrease.

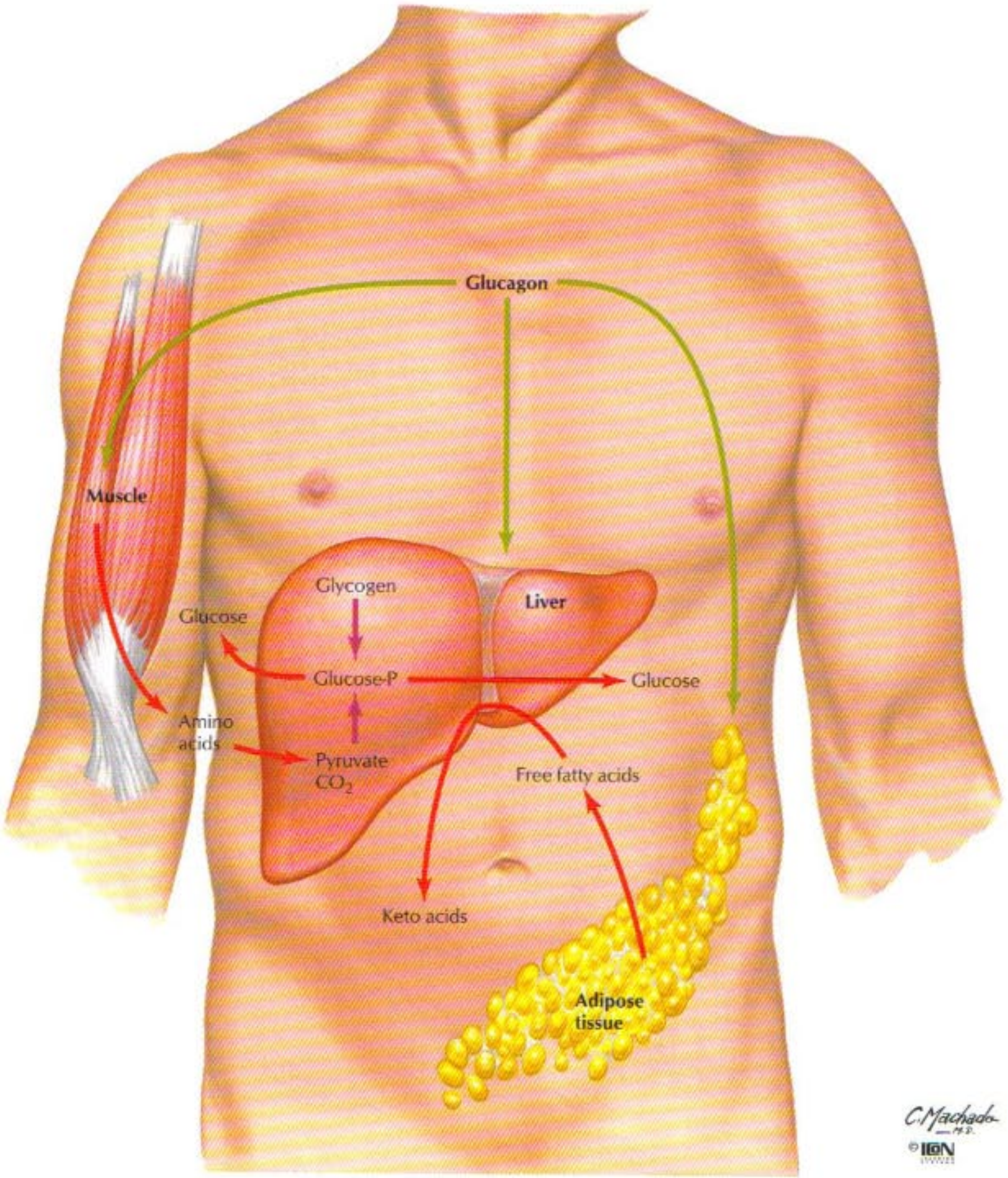
Glucagon
Muscle
Glycogen
Liver
Glucose
Glucose-P
Glucose
Amino acids
Pyruvate CO_2
Free fatty acids
Keto acids
Adipose tissue
C.Machado M.D.
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FIGURE 8.21 ACTIONS OF GLUCAGON

Glucagon is a fuel-mobilization hormone. It acts on the liver to break down glycogen and stimulates hepatic gluconeogenesis from amino acids. The effect of these actions is to increase the blood glucose concentration. Glucagon also acts on adipose tissue to stimulate lipolysis and the release of fatty acids. Metabolism of the fatty acids by the liver produces keto acids. Amino acids are released from muscle in response to glucagons and are converted to glucose in the liver by gluconeogenesis. The net effect of glucagon is that glucose, fatty acid, and keto acid levels in the blood increase.

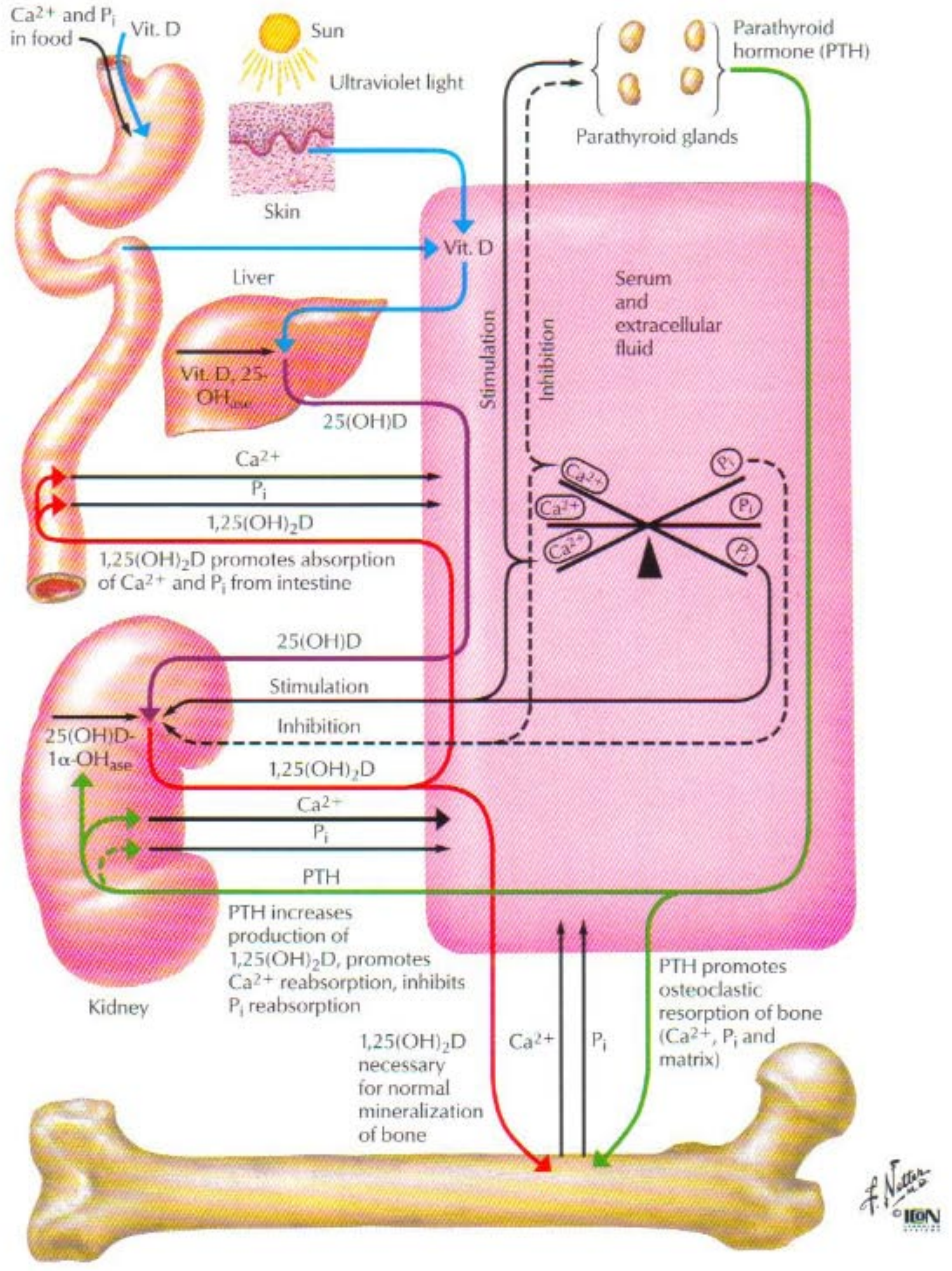
Ca^{2+} and P_i in food
Vit. D
Sun
Ultraviolet light
Skin
Parathyroid hormone (PTH)
Parathyroid glands
Vit. D
Liver
Vit. D, 25-OH_{ase}
25(OH)D
Stimulation
Inhibition
Serum and extracellular fluid
Ca^{2+}
P_i
$1,25(OH)_2D$
$1,25(OH)_2D$ promotes absorption of Ca^{2+} and P_i from intestine
25(OH)D
Stimulation
Inhibition
25(OH)D-1α-OH_{ase}
$1,25(OH)_2D$
Ca^{2+}
P_i
PTH
PTH increases production of $1,25(OH)_2D$, promotes Ca^{2+} reabsorption, inhibits P_i reabsorption
Kidney
$1,25(OH)_2D$ necessary for normal mineralization of bone
Ca^{2+}
P_i
PTH promotes osteoclastic resorption of bone (Ca^{2+}, P_i and matrix)
F. Netter
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FIGURE 8.22 PARATHYROID HORMONE

The parathyroid glands secrete parathyroid hormone (PTH) in response to a decrease in the ionized [Ca^{2+}] of the blood. PTH acts on bone to cause resorption and release of Ca^{2+}. Renal reabsorption of Ca^{2+} is also stimulated by PTH (see Figure 6.16). PTH alters vitamin D metabolism. Vitamin D is a sterol produced in the skin and absorbed from the diet. It undergoes metabolic conversions in the liver and kidneys. PTH acts on the kidneys to stimulate the conversion of 25(OH)-vitamin D to the active form of the hormone, 1,25-$(OH)_2$-vitamin D (an increase blood P_i also stimulates this conversion). The increased levels of 1,25-$(OH)_2$-vitamin D in turn stimulate the intestinal absorption of Ca^{2+}. The net effect of these actions is that PTH increases the ionized [Ca^{2+}] of the blood. PTH also causes the release of phosphate (P_i) from the bone and enhances its absorption from the GI tract. However, much of this P_i is excreted in the urine, because PTH also decreases renal P_i reabsorption (see Figure 6.16). Thus, the [P_i] of the blood is not significantly changed.

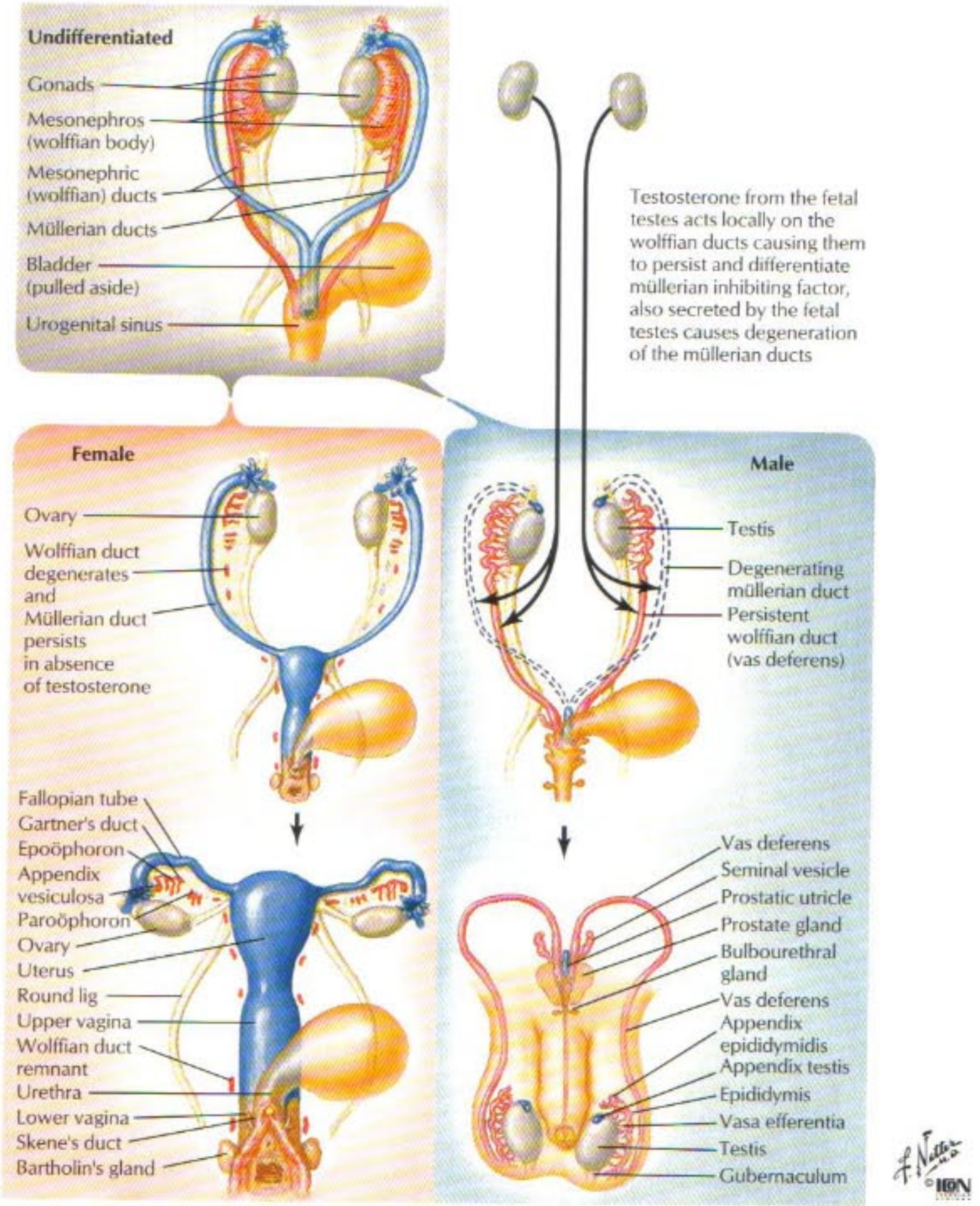
Undifferentiated
Gonads
Mesonephros (wolffian body)
Mesonephric (wolffian) ducts
Müllerian ducts
Bladder (pulled aside)
Urogenital sinus
Testosterone from the fetal testes acts locally on the wolffian ducts causing them to persist and differentiate müllerian inhibiting factor, also secreted by the fetal testes causes degeneration of the müllerian ducts
Female
Ovary
Wolffian duct degenerates and Müllerian duct persists in absence of testosterone
Fallopian tube
Gartner's duct
Epoöphoron
Appendix vesiculosa
Paroöphoron
Ovary
Uterus
Round lig
Upper vagina
Wolffian duct remnant
Urethra
Lower vagina
Skene's duct
Bartholin's gland
Male
Testis
Degenerating müllerian duct
Persistent wolffian duct (vas deferens)
Vas deferens
Seminal vesicle
Prostatic utricle
Prostate gland
Bulbourethral gland
Vas deferens
Appendix epididymidis
Appendix testis
Epididymis
Vasa efferentia
Testis
Gubernaculum
F. Netter
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FIGURE 8.23 GONAD AND GENITAL DUCT FORMATION

Based on the expression of specific gene products under the control of the sex chromosomes (X and Y chromosomes), the undifferentiated gonads and duct system of the human embryo develop along the male or female lineage (the exact role of these gene products [SRY and DAX-1 genes] are still being investigated). In the presence of SRY gene expression (46XY complement of chromosomes), the fetal testes develop and produce testosterone, which acts locally on the mesonephric (wolffian) duct system (shown in red), which persists and develops into the efferent ductules, epididymis, vas deferens, ejaculatory ducts, and the seminal vesicles. The paramesonephric (müllerian) ducts degenerate in response to a hormone called müllerian-inhibiting substance secreted by the fetal testes. In the absence of testosterone, the gonads of a normal female fetus (46XX complement of chromosomes) differentiate into paired ovaries, and the paramesonephric duct system (shown in blue in the left panels) persists while the mesonephric ducts degenerate. The paramesonephric ducts gives rise to paired uterine (fallopian) tubes, a midline uterus, and the upper portion of the vagina.

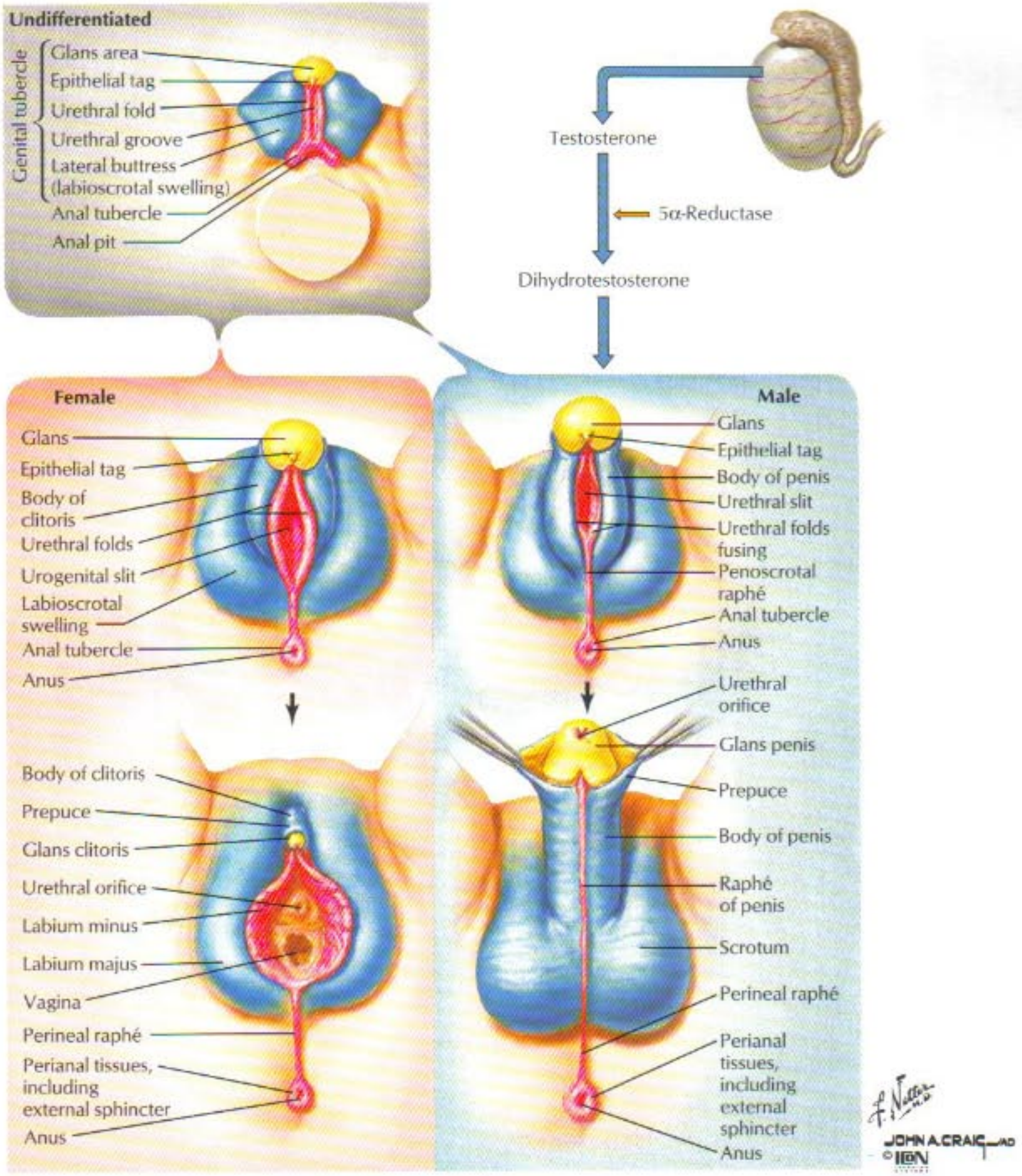
Undifferentiated
Genital tubercle
Glans area
Epithelial tag
Urethral fold
Urethral groove
Lateral buttress (labioscrotal swelling)
Anal tubercle
Anal pit
Testosterone
5α-Reductase
Dihydrotestosterone
Female
Glans
Epithelial tag
Body of clitoris
Urethral folds
Urogenital slit
Labioscrotal swelling
Anal tubercle
Anus
Body of clitoris
Prepuce
Glans clitoris
Urethral orifice
Labium minus
Labium majus
Vagina
Perineal raphé
Perianal tissues, including external sphincter
Anus
Male
Glans
Epithelial tag
Body of penis
Urethral slit
Urethral folds fusing
Penoscrotal raphé
Anal tubercle
Anus
Urethral orifice
Glans penis
Prepuce
Body of penis
Raphé of penis
Scrotum
Perineal raphé
Perianal tissues, including external sphincter
Anus
F. Netter M.D.
JOHN A.CRAIG_AD
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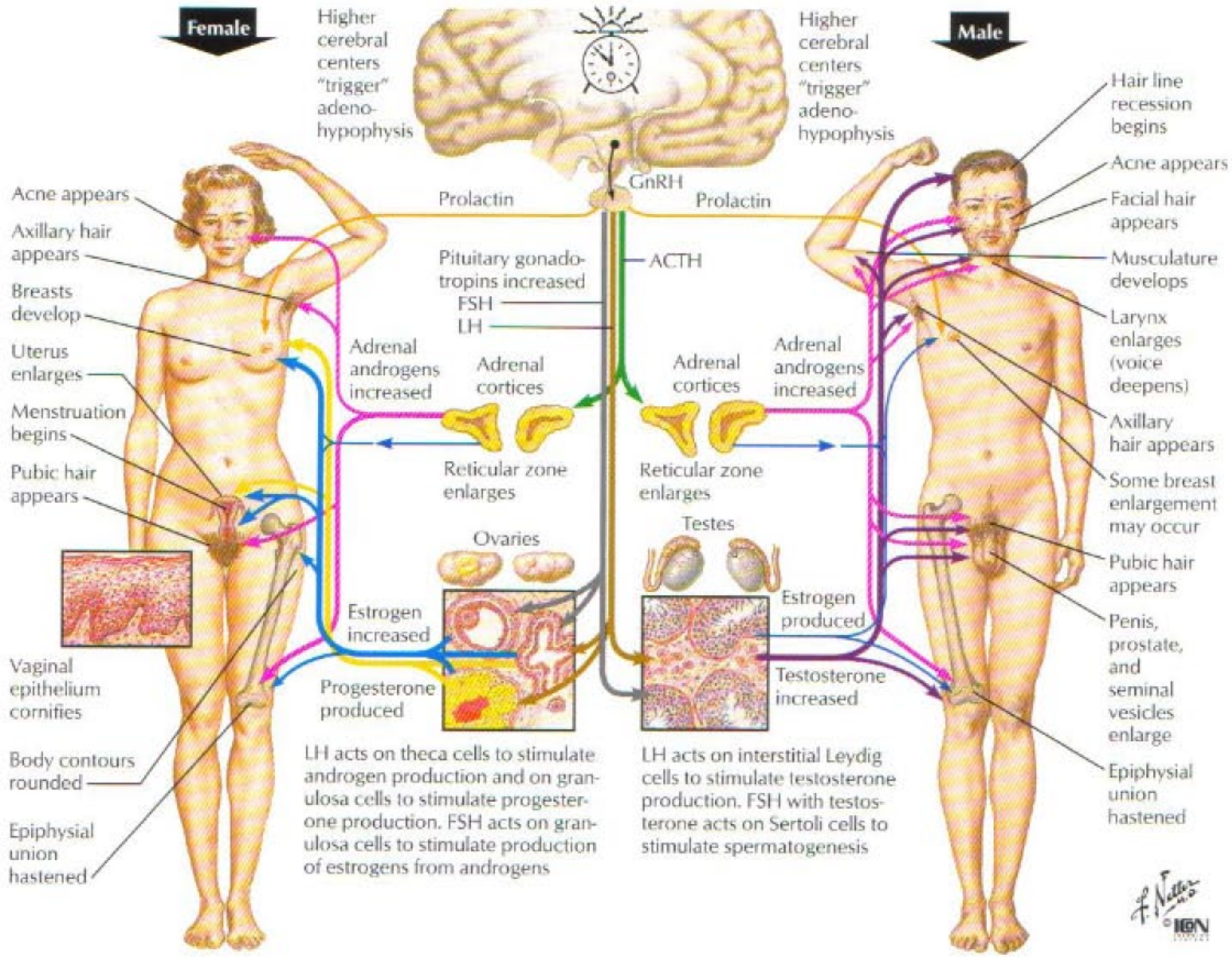
Figure 8.24 Differentiation of the External Genitalia

During early embryonic development, the external genitalia are undifferentiated and consist of tissue swellings comprised of the genital tubercle and urethral and anal folds. Under the influence of dihydrotestosterone, the genital tubercle elongates to form the phallus (glans) and normal male external genital development proceeds. In the absence of testicular androgens, the undifferentiated genitalia develop into those of a normal female. The color scheme of this figure clearly shows the homologous structures of the external genitalia between the two sexes.


Female
Higher cerebral centers "trigger" adenohypophysis
Higher cerebral centers "trigger" adenohypophysis
Male
GnRH
Prolactin
Prolactin
Pituitary gonadotropins increased
FSH
LH
ACTH
Adrenal androgens increased
Adrenal cortices
Adrenal cortices
Adrenal androgens increased
Reticular zone enlarges
Reticular zone enlarges
Ovaries
Testes
Estrogen increased
Progesterone produced
Estrogen produced
Testosterone increased
Acne appears
Axillary hair appears
Breasts develop
Uterus enlarges
Menstruation begins
Pubic hair appears
Vaginal epithelium cornifies
Body contours rounded
Epiphysial union hastened
Hair line recession begins
Acne appears
Facial hair appears
Musculature develops
Larynx enlarges (voice deepens)
Axillary hair appears
Some breast enlargement may occur
Pubic hair appears
Penis, prostate, and seminal vesicles enlarge
Epiphysial union hastened
F. Netter M.D.
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LH acts on theca cells to stimulate androgen production and on granulosa cells to stimulate progesterone production. FSH acts on granulosa cells to stimulate production of estrogens from androgens

LH acts on interstitial Leydig cells to stimulate testosterone production. FSH with testosterone acts on Sertoli cells to stimulate spermatogenesis

FIGURE 8.25 PUBERTY

One to two years before puberty, adrenal androgen levels increase (adrenarche). These adrenal androgens are responsible, in both sexes, for the early development of pubic and axillary hair and increased growth. At puberty, the hypothalamus increases the frequency and amount of gonadotropin-releasing hormone (GnRH) released. GnRH in turn stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary. In the male, LH acts on the interstitial Leydig cells of the testes to stimulate the production of testosterone. FSH together with testosterone acts on the Sertoli cells of the testes, which are important for support and development of the spermatozoa. In the female, LH acts on both the theca and granulosa cells of the ovary. In response to LH, the theca cells produce androgens, which are then converted to estrogens by the granulosa cells. LH acts on the granulosa cells to stimulate progesterone production. FSH acts on the granulosa cells to stimulate the production of estrogens from androgens.

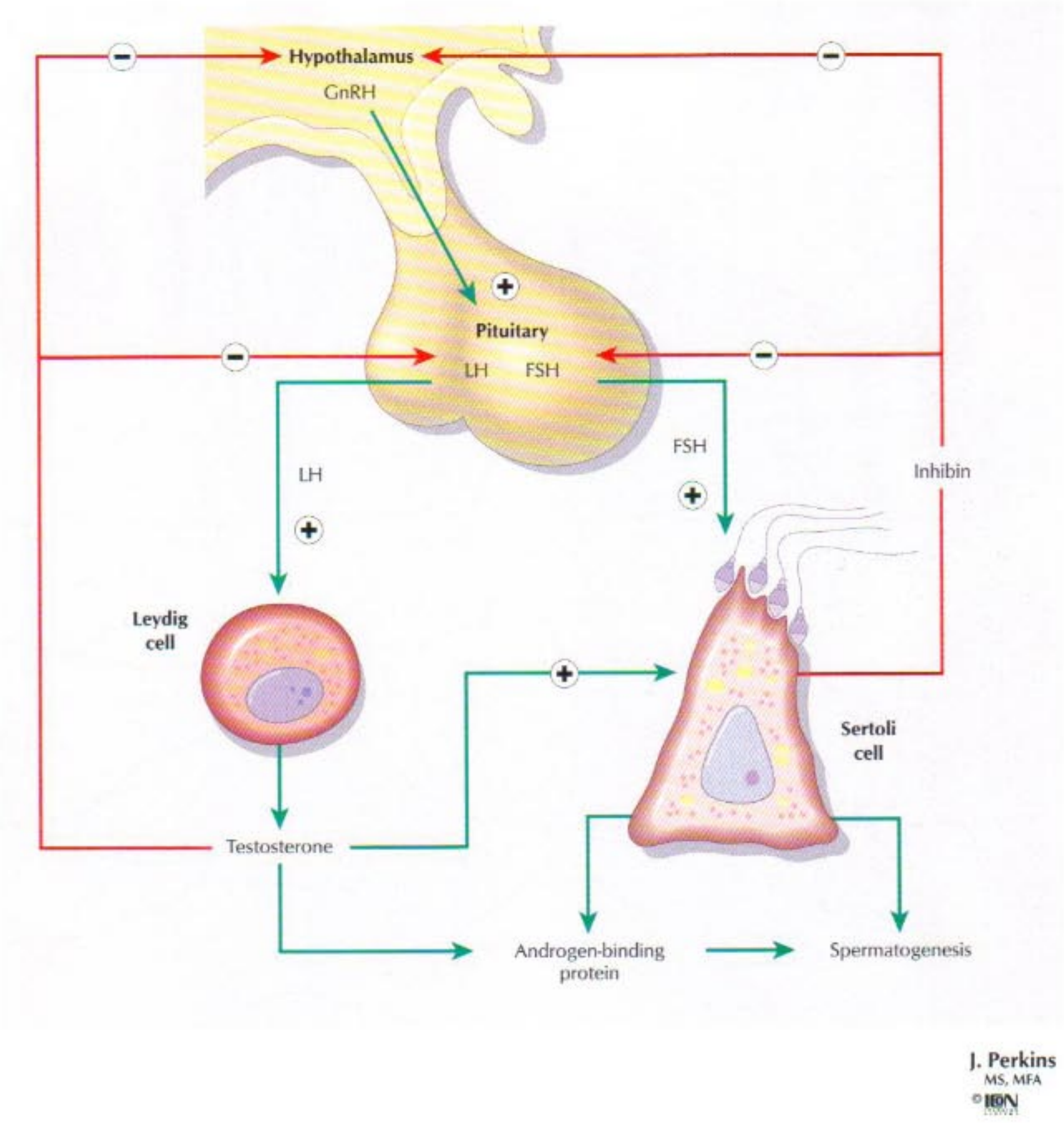
−
Hypothalamus
−
GnRH
+
Pituitary
−
LH
FSH
−
FSH
LH
+
Inhibin
+
Leydig cell
+
Sertoli cell
Testosterone
Androgen-binding protein
Spermatogenesis
J. Perkins MS, MFA
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FIGURE 8.26 CONTROL OF TESTICULAR FUNCTION

The testes are under the control of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and their secretion from the anterior pituitary is controlled by gonadotropin-releasing hormone (GnRH) from the hypothalamus. LH acts on the interstitial Leydig cells to stimulate their production of testosterone. FSH acts on the Sertoli cells to stimulate their production of androgen-binding protein, which then concentrates testosterone in the seminiferous tubules and thereby supports and promotes spermatogenesis. Testosterone provides negative feedback inhibition of LH release, whereas inhibin produced by the Sertoli cells provides negative feedback inhibition of FSH secretion.

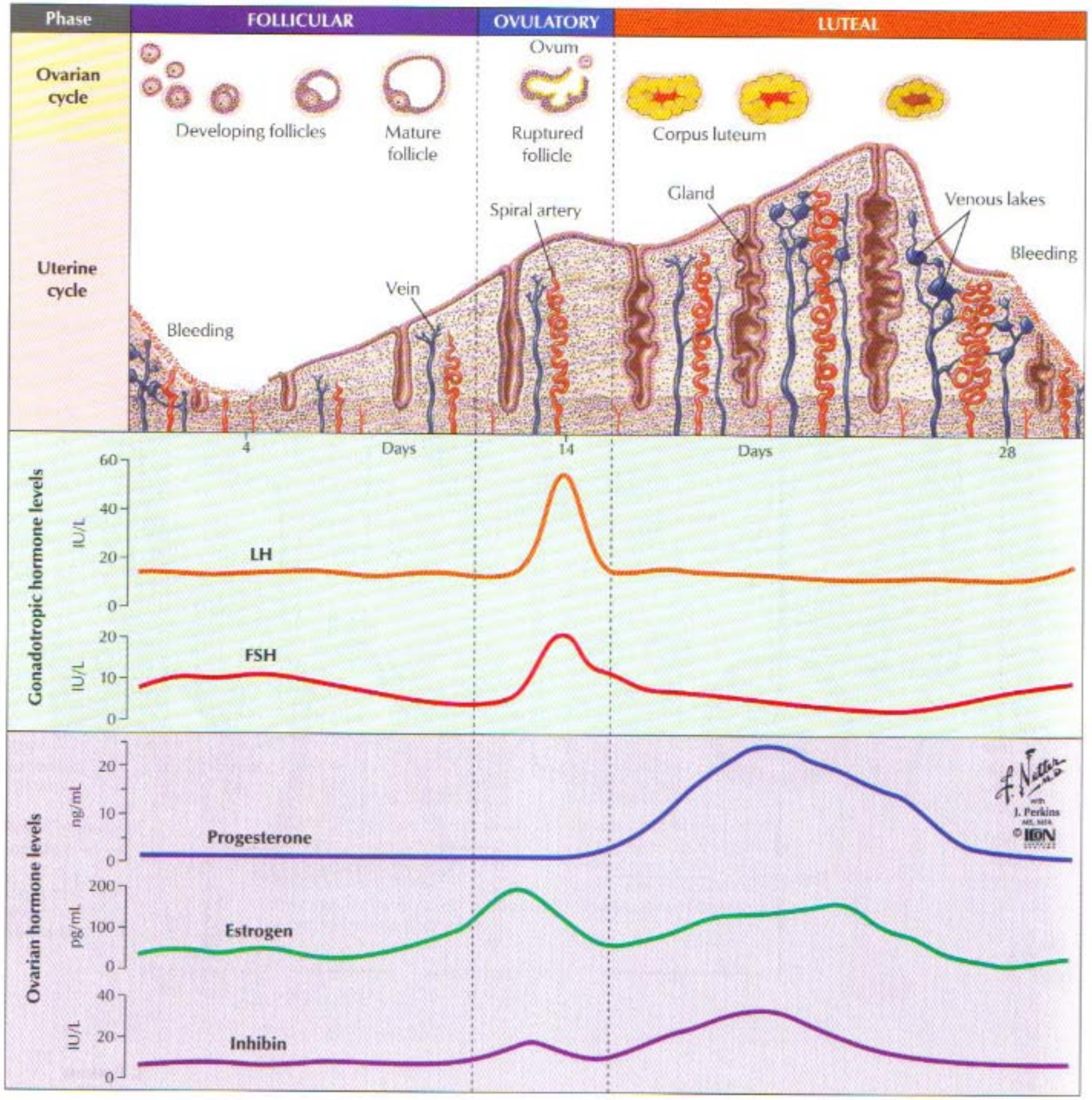
Phase
FOLLICULAR
OVULATORY
LUTEAL
Ovarian cycle
Ovum
Developing follicles
Mature follicle
Ruptured follicle
Corpus luteum
Gland
Spiral artery
Venous lakes
Bleeding
Uterine cycle
Vein
Bleeding
4
Days
14
Days
28
Gonadotropic hormone levels
IU/L
60
40
20
0
LH
IU/L
20
10
0
FSH
Ovarian hormone levels
ng/mL
20
10
0
Progesterone
pg/mL
200
100
0
Estrogen
IU/L
40
20
0
Inhibin
F. Netter
with J. Perkins MS, MFA
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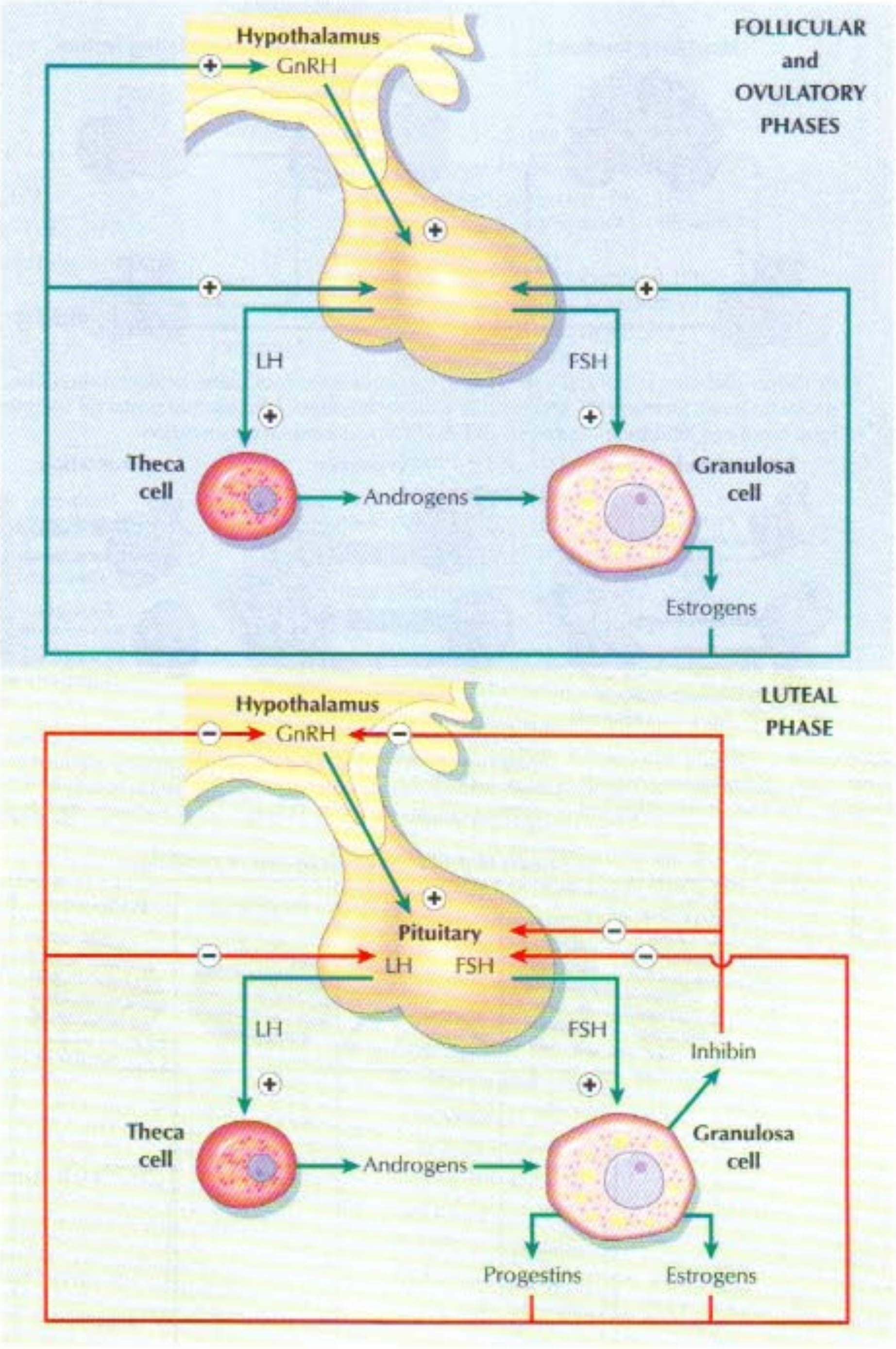
FIGURE 8.27 MENSTRUAL CYCLE

The menstrual cycle is divided into three phases: follicular, ovulatory, and luteal. The follicular phase begins during menses with the proliferation of the granulosa cells in a selected follicle. This is associated with rising levels of estradiol and, to a lesser extent, progestins, which feed back on both the hypothalamus and pituitary to stimulate (i.e., positive feed back) a surge in GnRH secretion followed by peaks in luteinizing (LH) and follicle-stimulating hormone (FSH) secretion, which then induce ovulation (see Figure 8.28).

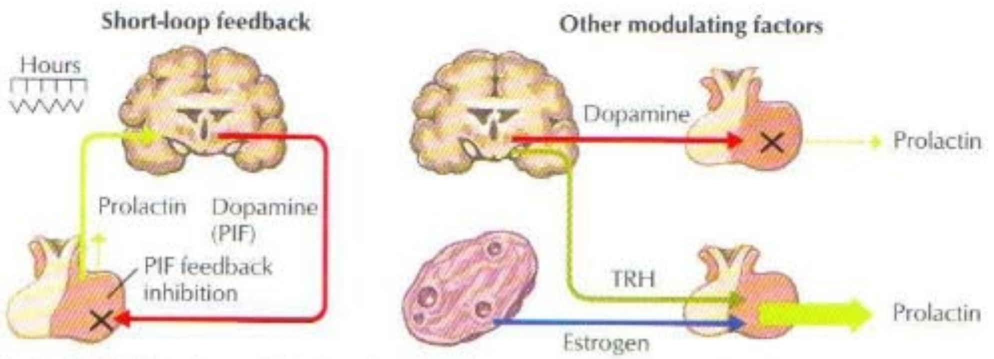
Following ovulation, the follicular cells transform into the corpus luteum and produce large amounts of progesterone and estradiol. During this luteal phase, the granulosa cells also produce inhibin. Together, progesterone, estradiol, and inhibin feed back on the pituitary to suppress LH and FSH secretion (see Figure 8.28). In the absence of fertilization of the released egg, the corpus luteum regresses and menses begins.


Hypothalamus
GnRH
FOLLICULAR and OVULATORY PHASES
LH
FSH
Theca cell
Androgens
Granulosa cell
Estrogens
Hypothalamus
GnRH
LUTEAL PHASE
Pituitary
LH
FSH
LH
FSH
Inhibin
Theca cell
Androgens
Granulosa cell
Progestins
Estrogens

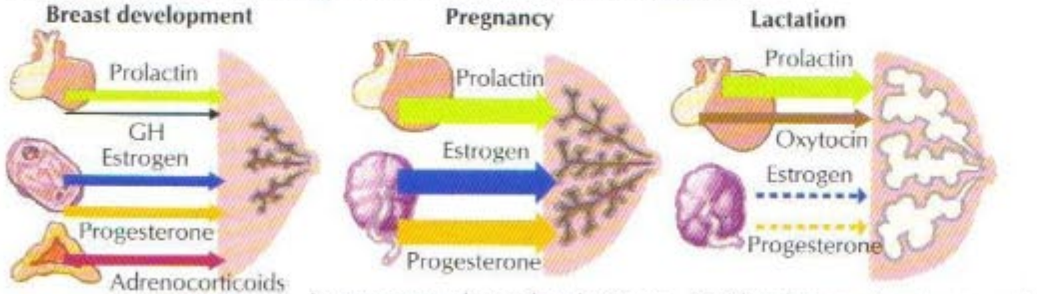
J. Perkins
MS, MFA

Figure 8.28 Hormonal Regulation of the Menstrual Cycle

Upper panel: During the follicular phase, the granulosa cells in a selected follicle proliferate and produce estradiol in response to follicle-stimulating hormone (FSH). At the same time, luteinizing hormone (LH) stimulates the theca cells to produce androgens. The androgens produced by the theca cells diffuse into the granulosa cells, where they are converted to estradiol. This leads to a large increase in estradiol production. The rising levels of estradiol and, to a lesser degree, progestins (e.g., progesterone), feed back on both the hypothalamus and pituitary to stimulate (i.e., positive feed back) a surge in GnRH secretion followed by peaks in LH and FSH secretion, which then induce ovulation. *Lower panel:* Following ovulation, the remaining follicular cells transform into the corpus luteum in response to LH and produce large amounts of progesterone and estradiol. During this luteal phase, the granulosa cells also produce inhibin. Together, progesterone, estradiol, and inhibin feed back on the pituitary to suppress LH and FSH secretion. In the absence of fertilization of the released egg, the corpus luteum regresses and menses begins.


Short-loop feedback
Hours
Prolactin
Dopamine (PIF)
PIF feedback inhibition
Other modulating factors
Dopamine
Prolactin
TRH
Estrogen
Prolactin

Prolactin-inhibiting factor (PIF), thought to be dopamine, modulates prolactin secretion. Elevated prolactin levels increase PIF secretion and cause feedback inhibition of prolactin secretion (short-loop feedback inhibition). Estrogen and TRH stimulate prolactin secretion


Breast development
Prolactin
GH
Estrogen
Progesterone
Adrenocorticoids
Pregnancy
Prolactin
Estrogen
Progesterone
Lactation
Prolactin
Oxytocin
Estrogen
Progesterone

Prolactin, along with GH, estrogen, progesterone, and adrenocorticoids, is necessary for breast development

In pregnancy, elevated prolactin, estrogen, and progesterone increase alveolobular development. High estrogen levels inhibit lactation

Sudden decrease in estrogen and progesterone in presence of prolactin results in milk production. Oxytocin stimulates milk release

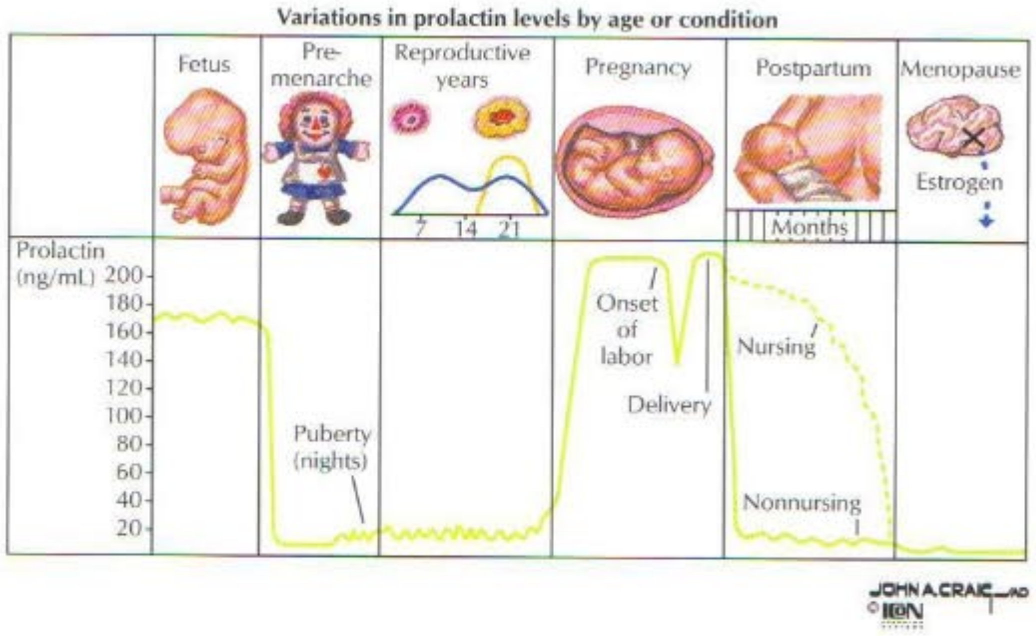


FIGURE 8.29 LACTATION

The role of prolactin in breast development, pregnancy, and lactation is summarized in this figure. Although prolactin is under dual hypothalamic control, it is unique because its secretion is under the inhibitory control of dopamine (PIF). *Abbreviation: GH,* Growth hormone.

When words alone won't do, think Netter

Netter's Atlas of Human Physiology

John T. Hansen, Ph.D. and Bruce M. Koeppen, M.D., Ph.D.

The Ideal *Companion Atlas* for any Physiology Course

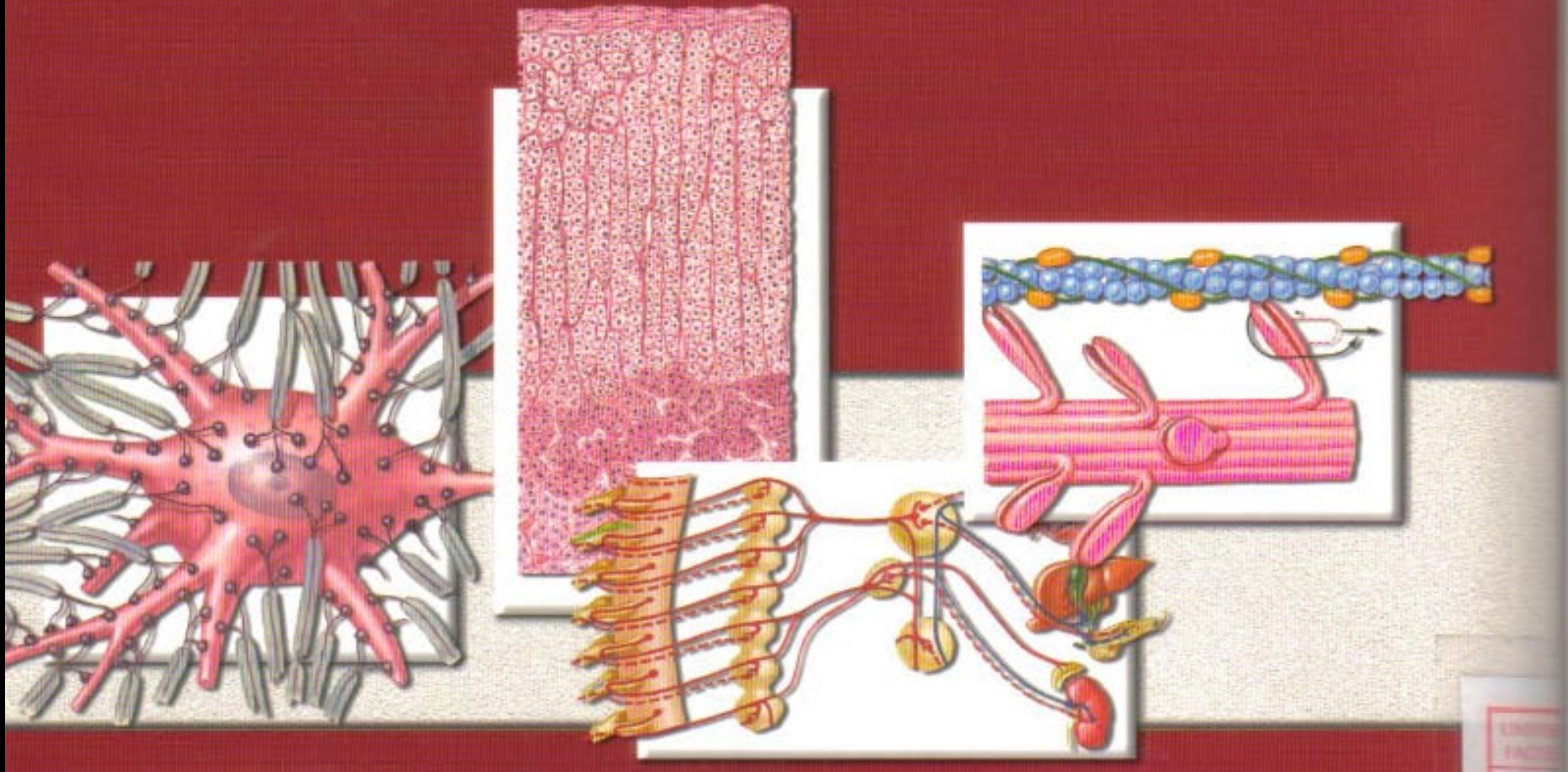
A clear, concise and user-friendly *Atlas* with a "big picture" approach to the study and review of major principles in human physiology.

In *Netter's Atlas of Human Physiology,* organ structure and function "come alive" with 250 of Dr. Frank H. Netter's beautifully rendered color drawings and schematics that enhance understanding of organ system physiology.

Each chapter leads the learner from the important overview relationships of organ system physiology down to the tissue, cell and subcellular levels. Graphs, charts and schematics illustrate key concepts and summarize integrated principles with visual clarity, making *Netter's Atlas of Human Physiology* the ideal companion to any physiology textbook.

Students and healthcare professionals will also find this Atlas useful for an overview of physiology principles, for USMLE review, or for patient education.

FEATURES INCLUDE:
- Summary of key concepts and principles
- Full color illustrations, schematics, graphs and charts
- Emphasis on structure-function relationships
- Brief captions that highlight key concepts
- Authored by two nationally recognized teachers



ISBN 192900701-9

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